

THE VASCULAR DISRUPTING AGENT OXI 4503 PREDOMINANTLY ENHANCES MILD HYPERTHERMIA.

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Background

Vascular Disrupting Agents (VDAs) exploit the differences between normal and tumour vasculature to selectively target tumour blood flow. Apart from killing tumour cells due to the ischemia induced, VDAs are also known to enhance the effect of other anti-cancer therapies, including hyperthermia. Combretastatin A-4 disodium phosphate is the leading VDA currently undergoing clinical testing. OXi 4503 is a new and more potent combretastatin derivative. The aim of this study is to investigate the ability of OXi 4503 to enhance heat treatment as a function of applied temperature.

Materials and Methods

Experiments were performed using a C3H mammary carcinoma tumour model grown subcutaneously in the rear right foot of female CDF1 mice. Treatments were performed when tumours reached a volume of 200 mm³. OXi 4503 was supplied by Oxigene Inc. (Watertown, MA, USA). It was administered as a single i.p. injection at 0.02 ml/g mouse. Non-anaesthetised mice were fixed in specially constructed jigs and local hyperthermia administered by submerging the tumour bearing foot in a thermostat controlled waterbath set at 0.2 °C higher than the prescribed temperature. Tumour volume was measured 5 times per week, and the time taken to reach 5 times the treatment volume (Tumour Growth Time; TGT) recorded. Statistical methods included t-tests and linear regression.

Results

The TGT for untreated tumours was 6.1 days. This was increased to 9.0 and 7.1 days following injection of an optimal dose of OXi 4503 (50mg/kg) and heating (41.5 °C; 60 min), respectively. Administering the OXi 4503 at 6, 3, 1, 0.5 and 0 hours before, and immediately after heating resulted in TGT-values of 12.1, 12.7, 12.6, 11.6, 11.3 and 10.8 days, respectively. The optimal interval of 3 hours was then used to combine OXi 4503 with different heat temperatures for different times. Slope values for the heat alone treatments increased exponentially with values of 3.6×10^{-4} (at 40.5 °C), 2.3×10^{-2} (at 41.5 °C) and 8.8×10^{-2} (at 42.5 °C) being obtained. With a preceding administration of OXi 4503 these slope values were increased to 3.0×10^{-2} (at 40.5 °C), 4.1×10^{-2} (at 41.5 °C) and 9.4×10^{-2} (at 42.5 °C). The increase was statistically significant at 40.5 °C and 41.5 °C, but not at 42.5 °C.

Conclusion

OXi 4503 enhanced the response of this C3H mammary carcinoma to heat. This enhancement was most pronounced at more clinically achievable mild hyperthermia temperatures.

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