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Preclinical Experimental Therapeutics

Therapeutic implications of tumor interstitial fluid pressure in subcutaneous RG-2 tumors¹

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Increased interstitial fluid pressure (IFP) in brain tumors results in rapid removal of drugs from tumor extracellular space. We studied the effects of dexamethasone and hypothermia on IFP in s.c. RG-2 rat gliomas, because they could potentially be useful as means of maintaining drug concentrations in human brain tumors. We used dexamethasone, external hypothermia, combined dexamethasone and hypothermia, and infusions of room temperature saline versus chilled saline. We measured tumor IFP and efflux half-time of ¹⁴C-sucrose from tumors. In untreated s.c. tumors, IFP was 9.1 ± 2.1 mmHg, tumor temperature was $33.7^\circ\text{C} \pm 0.7^\circ\text{C}$, and efflux half-time was 7.3 ± 0.7 min. Externally induced hypothermia decreased tumor temperature to $8.9^\circ\text{C} \pm 2.9^\circ\text{C}$, tumor IFP decreased to 3.2 ± 1.1 mmHg, and efflux half-time increased to 13.5 min. Dexamethasone decreased IFP to 2.4 ± 1.0 mmHg and increased efflux half-time to 15.4 min. Combined hypothermia and dexamethasone further increased the efflux half-time to 17.6 min. We tried to lower the tumor temperature by chilling the infusion solution, but at an infusion rate of 48 $\mu\text{l}/\text{min}$, the efflux rate was the same for room temperature saline and 15°C saline. The efflux rate was increased in both infusion groups, which suggests that efflux due to tumor IFP and that of the infusate were additive. Since lowering tumor IFP decreases efflux from brain tumors, it provides a means to increase drug residence time, which in turn increases the time-concentration exposure product of therapeutic drug available to tumor.

Key Words: brain tumor • chemotherapy • drug delivery • hypothermia • interstitial fluid pressure

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