Oleandrin inhibits the Na\(^+\), K\(^+\)-ATPase activity with an IC\(_{50}\) of 620 nM. Oleandrin induces apoptosis via activating endoplasmic reticulum stress.

IC\(_{50}\) & Target

IC\(_{50}\): 620 nM (Na\(^+\), K\(^+\)-ATPase)\(^1\).

In Vitro

Study of Na,K-ATPase inhibition shows an IC\(_{50}\) (nM) of 620 for Oleandrin. The inhibition of Na,K-ATPase by Oleandrin confirms that it likely exert its toxic effect through inhibition of sodium pump activity\(^1\). When treated with a series of concentrations of Oleandrin (0.2-25 nM), the undifferentiated CaCO-2 cells are sensitive as evidenced by an IC\(_{50}\) of 8.25 nM. In contrast, a maximum growth inhibition of only 20% is reached in differentiated CaCO-2 cells even though they are treated with Oleandrin concentrations as high as 25 nM\(^2\).

In Vivo

The effect of Oleandrin is investigated on glioma growth in vivo. To this aim, SCID or C57BL/6 mice are transplanted, respectively, with human U87MG (5×10\(^4\)), U251, GBM19 (5×10\(^5\)), or murine (syngeneic) GL261 (7.5×10\(^4\)) cells into the right striatum and, after 10 d, treated daily with intraperitoneal Oleandrin for an additional 7 d. Oleandrin significantly reduces tumor sizes in human and murine glioma cell models in vivo in a dose-dependent way. High concentrations of Oleandrin (3 mg/kg) are fatal in both models, as expected from the known lethal dose for rodents. Doses of Oleandrin below the lethal dose (0.3 mg/kg) significantly increase the survival time from 32.6±1.4 d to 53.8±9.6 d in mice injected with U87MG cells (n=5-11; p<0.01, log-rank test) and from 23.37±1.2 d to 34.38±3.3 d (n=5-11; p<0.01, log rank test) in mice injected with GL261 cells\(^3\).

PROTOCOL

Cell Assay\(^2\)

Undifferentiated wild-type and well-differentiated CaCO-2 cells are treated with a range of concentrations of Oleandrin (0.2-25 nM). After 48 h, cells are labeled with BrdU and relative cell proliferation is determined with a BrdU Cell Proliferation Kit\(^2\).

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal

Mice\(^3\)
After tumor cell injection, SCID or C57BL/6 mice are monitored daily. The end point is determined by lack of physical activity or death. The mean survival time is calculated using the Kaplan-Meier method and statistical analysis is performed using a log-rank test. For cotreatment with Temozolomide (TMZ), 10 d after tumor injection, mice are treated with Oleandrin (0.03, 0.3, or 3 mg/kg/daily, i.p.), TMZ (50 mg/kg, i.p., every 2 d for a total of 4 times with a stop of 2 weeks) or both. The dosing scheme is chosen starting from these data to be reasonably sure that a constant concentration of drug is maintained along the experiment. Animals used in Kaplan-Meier survival studies receive up to four TMZ cycles.

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