Salinomycin increases chemosensitivity to the effects of doxorubicin in soft tissue sarcomas.

Chemotherapy for soft tissue sarcomas remains unsatisfactory due to their low chemosensitivity. Even the first line chemotherapeutic agent doxorubicin only yields a response rate of 18-29%. The antibiotic salinomycin, a potassium ionophore, has recently been shown to be a potent compound to deplete chemoresistant cells like cancer stem like cells (CSC) in adenocarcinomas. Here, we evaluated the effect of salinomycin on sarcoma cell lines, whereby salinomycin mono- and combination treatment with doxorubicin regimens were analyzed. To evaluate the effect of salinomycin on fibrosarcoma, rhabdomyosarcoma and liposarcoma cell lines, cells were drug exposed in single and combined treatments, respectively. The effects of the corresponding treatments were monitored by cell viability assays, cell cycle analysis, caspase 3/7 and 9 activity assays. Further we analyzed NF-κB activity; p53, p21 and PUMA transcription levels, together with p53 expression and serine 15 phosphorylation. The combination of salinomycin with doxorubicin enhanced caspase activation and increased the sub-G1 fraction. The combined treatment yielded higher NF-κB activity, and p53, p21 and PUMA transcription, whereas the salinomycin monotreatment did not
Salinomycin increases the chemosensitivity of sarcoma cell lines - even at sub-lethal concentrations - to the cytostatic drug doxorubicin. These findings support a strategy to decrease the doxorubicin concentration in combination with salinomycin in order to reduce toxic side effects.