Effects of NO and H2S releasing doxorubicin on a xenograft model of chemoresistant prostate cancer

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Prostate cancer is the most prevalent cancer in men worldwide. Advanced diseases are commonly treated with androgen deprivation therapy however patients progress into castration-resistant prostate cancer, which is the most aggressive and lethal form of prostate cancer. In these patients, chemotherapy is not effective due the onset of drug resistance mediated by P-glycoprotein p (Pgp) overexpression, consequently, the prognosis is poor. We developed synthetic doxorubicins, containing NO and H2S-releasing groups (DR6 and CC2790A) that showed an high cytotoxicity on in vitro model of doxorubicin-resistant prostate cancer cells (DU-145). DU-145 cells were injected (4*106 for animal) in nude mice (Nude-Foxn1nu/Foxn1+). Animals were divided in to four groups and treated for three weeks with vehicle, doxorubicin, DR6 and CC2790A (5mg/kg) respectively. During and after treatment animal weight, tumor volume, drugs accumulation in the tumors, the percentage of apoptotic cells, the presence of nytrotyrosine residues and SH groups in the tumors and the left ventricular wall thickness were evaluated. DR6 and CC2790A induced a reduction of 60% of tumor volumes, while doxorubicin didn't exert any effect. The drugs auto-fluorescence revealed an high accumulation of our drugs within the tumor masses. In fact DR6 and CC2790A, as opposed of doxorubicin, increased the presence of apoptotic cells in both the inner and the outer part of the tumors. The treatment with DR6 and CC2790A increased the presence of nytrotyrosine and SH groups in the tumor masses respectively, suggesting a possible mechanism of Pgp inhibition. Regarding the cardio-toxic side effects, doxorubicin caused two deaths during treatment and significantly increased the left ventricular wall thickness. On the contrary, the treatment with DR6 and CC2790A did not show either macroscopic or microscopic evidences of toxicity. DR6 and CC2790A are potential novel therapeutic strategies against chemoresistant prostate cancer combining efficacy with reduced cardiovascular side effects. By proposing an innovative strategy to reverse chemotherapy resistance, our study suggests a new tool against androgen independent prostate cancer, aiming at ameliorating the prognosis and improving the quality of life of a significant proportion of patients.

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