ABSTRACT

Lobeline enhances chemosensitivity of doxorubicin in multidrug-resistant human uterine sarcoma cells

Mei-Chen Shen, Chin-Hsun Hsu

Background: Drug resistance remains a major clinical challenge for cancer treatment. Multidrug resistance (MDR) can limit efficacy of chemotherapy. The well-studied mechanism involves P-gp (P-glycoprotein) mediated drug efflux. P-gp is a Mr ~170,000 member of the ABC-type transporter family and functions as an energy-dependent membrane efflux pump that transports a wide variety of structurally unrelated xenobiotics to maintain cytoplasmic concentrations at subtoxic levels. P-gp is also responsible for decreased drug accumulation in multidrug-resistant cells and often mediates the development of resistance to anticancer drugs, such as doxorubicin. Lobeline, a piperidine alkaloid, which is produced by Lobelia inflata (family Lobeliaceae) and several other Lobelia species, stimulates chemoreceptors in carotid and aortic bodies, and then exerts reflexory activation of respiratory center. In 2008, Ma et al have mentioned that MDR reversal potential of lobeline could be demonstrated in cells treated with doxorubicin in that lobeline can sensitize resistant tumor cells at non-toxic concentrations. Here, we aim to test whether lobeline could sensitize doxorubicin resistant cancer cells.

Materials and Methods: The human doxorubicin resistant uterine sarcoma cells (MES-SA/Dx5 cells) were doxorubicin induced P-gp over-expressed MDR sublines of human uterine carcinoma MES-SA cells respectively. The MES-SA/Dx-5 cells expressing high levels of P-gp were treated with different doxorubicin concentrations in the presence or absence of lobeline. Cell cytotoxicity was evaluated by MTT assay. To study the effects of doxorubicin combined with lobeline, we used real-time PCR and western blot to determine the expression of ABCB1 in MES-SA or MES-SA/Dx-5 treated with doxorubicin and lobeline, respectively.

Results: Our results showed that lobeline had no toxicity in MES-SA and MES-SA/Dx-5, evaluated by MTT assay. But lobeline had significant suppression effect in MES-SA/Dx-5 treated with doxorubicin, compared to MES-SA. MTT assay showed that after treatment with 5 and 10 μM doxorubicin for 24 h, the survival rates of MES-SA/Dx5 cells were 79.56±4.98% and 74.18±3.31%, while treated in combination with 50 μM lobeline, the cell survival rates were 67.01±1.24% and 60.29±2.53%, respectively (p < 0.05). When we treated lobeline combined with doxorubicin in MES-SA/Dx-5, mRNA of MDR1 suppression rate was significantly decreased on the third day after treatment. The suppression effect could also be confirmed by western blot.

Discussion: The major drawbacks associated with doxorubicin therapy are the dose-limiting toxicity and development of drug resistance, which warrants innovative strategies that can ensure the optimal use of this frontline chemotherapeutic agent in clinic. Lobeline might have the potential to treat the drug resistant cancer cells combined with anticancer drug. We will use drug accumulation assay to clarify the efficacy of lobeline in future. The confirmation of the synergistic effect of doxorubicin and lobeline in this clinically relevant model signifies the therapeutic potential of the synergism.