Metformin, at concentrations corresponding to the treatment of diabetes, potentiates the cytotoxic effects of carboplatin in cultures of ovarian cancer cells

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Abstract

The use of the type 2 diabetics drug metformin has been correlated with enhanced progression-free survival in ovarian cancer. The literature has speculated that this enhancement is due to the high concentration of metformin directly causing cancer cell death. However, this explanation does not fit with clinical data reporting that the women exposed to constant micromolar concentrations of metformin, as present in the treatment of diabetes, respond better to chemotherapy. Herein, our aim was to examine whether micromolar concentrations of metformin alone could bring about cancer cell death and whether micromolar metformin could increase the cytotoxic effect of commonly used chemotherapies in A2780 and SKOV3 cell lines and primary cultured cancer cells isolated from the peritoneal fluid of patients with advanced ovarian cancer. Our results in cell lines demonstrate that no significant loss of viability or change in cell cycle was observed with micromolar metformin alone; however, we observed cytotoxicity with micromolar metformin in combination with chemotherapy at concentrations where the chemotherapy alone produced no loss in viability. We demonstrate that previous exposure and maintenance of metformin in conjunction with carboplatin produces a synergistic enhancement in cytotoxicity of A2780 and SKOV3 cells (55% and 43%, respectively). Furthermore, in 5 (44%) of the 11 ovarian cancer primary cultures, micromolar metformin improved the cytotoxic response to carboplatin but not paclitaxel or doxorubicin. In conclusion, we present data that support the need for a clinical study to evaluate the adjuvant maintenance or prescription of currently approved doses of metformin during the chemotherapeutic treatment of ovarian cancer..

Keywords

Chemotherapy, Doxorubicin, Paclitaxel.