

SEQUENCED COMBINATIONS OF PLATINUM DRUGS WITH BORTEZOMIB IN OVARIAN TUMOUR MODELS

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Background and Aims

Although widely used in the clinic, drug resistance is a constant problem with platinum drugs such as cisplatin and carboplatin, especially in the ovarian cancer. Cisplatin hinders its own uptake by inducing proteasomal degradation of the influx carrier copper transporter 1 (CTR1). Proteasome inhibitor bortezomib (BORT) –an anticancer drug on its own right – is found to block such degradation so that in the presence of the inhibitor cellular uptake of platinum and consequently the level of platinum–DNA binding may be increased resulting in enhanced cell death.

Methods

In this study efficacy from the sequenced combinations of cisplatin, carboplatin and oxaliplatin with BORT in the human ovarian A2780, A2780^{cisR}, A2780^{ZD0473R} and SKOV-3 cancer cell lines was evaluated. The levels of cellular platinum accumulation and platinum–DNA binding as well as the levels of total and oxidized glutathione were determined. Finally, changes in expression of key proteins associated with drug resistance were determined using proteomics.

Results

Presence of BORT is found to enhance cellular accumulation of platinum, the level of Platinum–DNA binding and also the oxidative stress especially in the resistant cell lines. Expression of over thirty proteins associated with drug resistance was found to be altered by the selected combinations.

Conclusions

Combinations of platinum drugs with BORT are found to increase cellular accumulation of platinum and the level of platinum–DNA binding, increase oxidative stress, and alter expressions of key proteins associated with drug resistance.