

Maximising the effect of platinum drugs in ovarian tumour models

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Abstract

Background: Ovarian cancer remains an on-going challenge primarily because of the development of drug resistance and also because the cancer is likely to have metastasized at the time of diagnosis. Currently, chemotherapy based on platinum drugs such as cisplatin is the primary treatment for the disease. The multi-factorial nature of platinum resistance enables the use of different strategies to overcome the mechanisms of resistance. The increase of cellular platinum accumulation, prevention the deactivation of platinum drugs, increasing the level of platinum–DNA binding and reducing tolerance of platinum–DNA adducts can be employed to overcome resistance.

Cisplatin is thought to enter the cell by carrier-mediated transport and passive diffusion. One influx carrier for cisplatin is the copper transporter CTR1. However, cisplatin triggers the down-regulation of CTR1 through proteasomal degradation. Bortezomib, a proteasome inhibitor, is found to retard cisplatin-induced down-regulation of CTR1 so that in the presence of bortezomib, the cellular uptake of cisplatin and consequently the level of its binding with the DNA may be increased.

Methods: In this study synergism in activity from the sequenced combination of cisplatin, carboplatin and oxaliplatin with bortezomib in the human ovarian A2780, A2780^{cisR} and A2780^{ZD0473R} cancer cell lines have been investigated.

Results: The results show that in presence of bortezomib both cellular accumulation of platinum and the level of platinum–DNA are increased in line with the idea of protective role played by bortezomib against cisplatin-induced CTR1 degradation. However, the increased in activity of platinum drugs due to the presence of bortezomib appears to be less clear cut.

Conclusion: The results suggest that the prevention of CTR1 degradation by bortezomib may be playing a major role in increasing the cellular uptake of cisplatin and platinum–DNA binding level.

Keywords: Cisplatin, ovarian cancer, bortezomib, drug resistance, sequenced combination