ABSTRACT SUBMISSION

TITLE

AIMING TO MAXIMISE ANTITUMOUR ACTIVITY OF PLATINUM DRUGS IN OVARIAN TUMOUR MODELS

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ABSTRACT TEXT

Platinum drugs such as cisplatin and its analogues carboplatin and oxaliplatin are routinely used in the clinic to kill cancerous cells. However, the use of the drugs has been associated with the development of drug resistance and severe toxicities. Because of the multi-factorial nature of platinum resistance, different strategies may be gainfully employed to overcome the mechanisms of resistance. These may include increasing the accumulation platinum within the cell, lowering the deactivation of platinum drug, increasing the level of platinum-DNA binding and reducing tolerance of platinum-DNA adducts. Transport of cisplatin into the cell is believed to take place by both passive diffusion and the use of carriers such as the copper transporter CTR1. However, cisplatin is found to trigger both the down-regulation and proteasomal degradation of CTR1. Bortezomib, a proteasome inhibitor, is found to inhibit cisplatin-induced down-regulation of CTR1 so that in the presence of bortezomib, cellular uptake of cisplatin and consequently the level of its binding with the DNA may be increased. In this study synergism in activity from the sequenced combination of cisplatin, carboplatin and oxaliplatin with bortezomib in the human ovarian A2780, $A2780^{cisR}$, $A2780^{ZD0473R}$ and SKOV-3 cancer cell lines has been investigated. The results show that the presence of bortezomib is indeed associated with increased intracellular accumulation of platinum and increased level of platinum–DNA binding. This is in line with the idea that the prevention of CTR1 degradation by bortezomib may be playing a significant role in increasing both platinum uptake and platinum-DNA binding level. However, the increase in activity from the combination appears to be less clear cut.