

## Ovarian cancer: new hope in current therapy

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### Abstract

Platinums such as cisplatin and its analogues carboplatin and oxaliplatin are routinely used in the clinic to kill cancerous cells. However, intrinsic and acquired resistance have limited the use of these drugs. Platinum resistance is multi-factorial. Mechanisms of resistance include decreased accumulation of platinum within the cell, increased deactivation of platinum drug, decreased level of platinum–DNA binding and increased tolerance of platinum–DNA adducts. This means that many different strategies may be gainfully employed to overcome the mechanisms of resistance. Cisplatin is believed to enter the cell by carrier-mediated transport, passive diffusion and pinocytosis. The copper transporter 1 CTR1 has been associated with the influx of cisplatin. However, cisplatin is found to trigger both the down-regulation and proteasomal degradation of this carrier. A proteasome inhibitor known as bortezomib has been found to retard cisplatin-induced down-regulation of CTR1. In the presence of bortezomib, cellular uptake of cisplatin and consequently the level of its binding with the DNA may be increased. Synergism in activity from the sequenced combination of cisplatin, carboplatin and oxaliplatin with bortezomib against the human ovarian A2780, A2780<sup>cisR</sup>, A2780<sup>ZD0473R</sup> and SKOV-3 cancer cell lines has been investigated. Generally the administration of bortezomib 2 h before that of the platinum drugs is found to produce the greatest cell kill, compared to bolus and the converse. This is best seen in the case of cisplatin. Furthermore, increased cell kill due to cisplatin and bortezomib is found to be associated with the increased intracellular platinum accumulation and increased platinum–DNA binding level. These findings suggest that the prevention of CTR1 degradation by bortezomib may be playing a key role in enhancing the cellular uptake of cisplatin, platinum-DNA binding level and eventually in cell death. The above results may have a profound clinical significance if found to be true *in vivo*. Work on the determination of cellular accumulation and platinum–DNA binding levels associated with the combinations of carboplatin and oxaliplatin with bortezomib are currently in progress.

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