Modulation of cisplatin cytotoxicity due to its combination with bortezomib and the nature of its administration.

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Abstract

The widely used anticancer drug cisplatin (CS) is believed to cross the cell membrane by passive diffusion, carrier-mediated transport and pinocytosis. One carrier involved in the transport of CS into the cell is the copper transporter CTR1. However, CS is found to trigger the down-regulation of CTR1 and its proteasomal degradation. The proteasome inhibitor bortezomib (Bort) has been reported to block CS-induced down-regulation of CTR1 so that in the presence of Bort, the cellular uptake of CS may be increased. Increased platinum accumulation may result in increased platinum-DNA binding so that CS in combination with Bort may produce pronounced cell kill. In this study, synergism in activity from the sequenced combination of CS and Bort in human ovarian A2780, A2780(cisR) and A2780(ZD0473R) cancer cell lines was studied. We also investigated the effect on cell kill due to the administration of CS in two aliquots with a time gap. Addition of Bort 2 h before CS was found to produce greater cell kill than the converse and the bolus, especially in the resistant A2780(cisR) and A2780(ZD0473R) cell lines, in line with increased platinum accumulation and platinum-DNA binding levels. Thus, the prevention of CTR1 degradation by Bort may play a significant role, especially in the resistant cell lines. Administration of CS in two aliquots with a time gap was also found to maximise the cell kill in the ovarian cancer cell lines. If such findings are found to be true in vivo, the results may be significant clinically.