



Current Medicinal Chemistry

ABSTRACTS

*The
International
journal for
timely
in - depth
reviews in
Medicinal
Chemistry*

An advertisement for a conference. It features a blue globe with a string of orange spheres (representing a polymer or drug chain) draped over it. The background is a complex network of grey and white spheres and lines, resembling a molecular structure or protein network. Several amino acid abbreviations are scattered around: "TM 5 Ser" at the top left, "Asp" at the top right, "Trp" at the bottom left, "Asn" at the bottom center, and "TM 7" at the bottom right. The central text reads:

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Conference on
Drug Discovery
& Therapy**
February 12 - 15, 2012, Dubai, UAE



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PO-126**MAXIMISING THE CELL KILL DUE TO PLATINUM DRUGS IN THE HUMAN OVARIAN TUMOUR MODELS****Zaynab Al-Eisawi, Fazlul Huq, Philip Beale, Charles Chan and Jun Qing Yu**

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Although cisplatin and its progeny carboplatin and oxaliplatin are routinely used in the clinic to kill cancerous cells, the use of the drugs has also been limited due to intrinsic and acquired resistance. Thus currently intense research effort is being applied with the aim of achieving means to overcome the drug resistance. The multi-factorial nature of platinum resistance means that many different strategies may be required or gainfully employed to overcome the mechanisms of resistance. These may include ways of increasing platinum accumulation within the cell, lowering of deactivation of platinum drug that constantly takes place before its binding with the DNA, increasing the level of platinum-DNA binding and reducing tolerance of platinum-DNA adducts. Cisplatin is believed to cross the cell membrane by carrier-mediated transport in addition to passive diffusion and pinocytosis. One carrier involved in the transport of cisplatin into the cell is the copper transporter CTR1. However, cisplatin is found to trigger the down-regulation of the carrier and its proteasomal degradation. Bortezomib, a proteasome inhibitor, has been reported to block cisplatin-induced down-regulation of CTR1 so that in the presence of the inhibitor cellular uptake of cisplatin and hence the level of its binding with the DNA may be increased. In this study synergism in activity from the sequenced combination of cisplatin and bortezomib in the human ovarian A2780, A2780^{cisR} and A2780^{ZD0473R} cancer cell lines has been investigated. Addition of bortezomib 2 h before that of cisplatin is found to produce a greater cell kill than the converse and the bolus, especially in the resistant A2780^{cisR} and A2780^{ZD0473R} cell lines, in line with the increased platinum accumulation and the platinum-DNA binding level. Thus the prevention of CTR1 degradation by bortezomib may be playing a significant role in increasing the cellular uptake of cisplatin, platinum-DNA binding level and eventually in the cell kill, especially in the resistant cell lines. We also investigated the effect on the cell kill due to the administration of cisplatin in two aliquots with a time gap. Since cisplatin brings about apoptosis by multiple pathways one of which may be more dominant than another depending on the status of the cell, it is thought that administration of cisplatin in two aliquots with a time gap may amount to the sequenced combination of two drugs with somewhat independent mechanisms of action and hence may produce synergistic outcomes. Indeed the administration of cisplatin in two aliquots with a time gap is found to maximise the cell kill in the human ovarian cancer cell lines. If found to be true *in vivo*, the above results may have a profound clinical significance.

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

PO-55

Track: Pharmaceutical Research & Development

A VALIDATED CAPILLARY ELECTROPHORESIS METHOD FOR SIMULTANEOUS DETERMINATION OF EZETIMIBE AND ATORVASTATIN IN PHARMACEUTICAL FORMULATIONS**Mona Mohammed AlShehri**

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Ezetimibe and atorvastatin are used for treating hypercholesterolemia. Clinical studies have shown that co-administration of ezetimibe plus atorvastatin was significantly more effective at reducing cholesterol and triglycerides than ezetimibe or atorvastatin alone, and the clinical use of these two agents as a combination is increasing continuously. Therefore, a simple, precise, and sensitive capillary electrophoresis technique coupled with a diode array detector has been developed for the separation and simultaneous determination of ezetimibe and atorvastatin in pharmaceutical formulations. Separation of both ezetimibe and atorvastatin was achieved utilizing fused silica capillary (58 cm x 75 µm ID) and background electrolyte solution that consisted of phosphate buffer (2.5 mM, pH 6.7): methanol (70:30 v/v). The proposed method was validated by testing its specificity, linearity, precision, accuracy, recovery, and detection