Tamoxifen enhances the cytotoxic effects of the nitrosourea fotemustine. Results on human melanoma cell lines.

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Abstract
Fotemustine (Fote) is a new amino acid-linked chloroethyl nitrosourea which has been shown to be useful in disseminated malignant melanoma. The aim of the present study was to analyse the cytotoxic effects resulting from the combination of anti-oestrogens and Fote on human melanoma cell lines. The anti-oestrogens tested were tamoxifen (TMX, 5 x 10(-7) mol/l and 5 x 10(-6) mol/l) and 4OH TMX (5 x 10(-8) mol/l and 5 x 10(-7) mol/l). As a preliminary step, a series of nine human melanoma cell lines was screened in order to identify and quantify the presence of oestradiol receptors (ER) in these cell lines. This led to the selection of an ER-positive (+) cell line. The drugs alone or in combination were then tested against CAL 1 ER (+) and CAL 7 ER (-) melanoma cell lines. Different sequences of drug combinations were tested using clinically compatible drug concentrations. For CAL 1 cells, there was a growth inhibitory effect induced by the anti-oestrogens given alone. Overall, the presence of the anti-oestrogens resulted in higher cytotoxic effects than when cells were exposed to Fote alone. The lowest IC50 Fote values as compared to Fote alone were generated by the sequences in which the anti-oestrogens were administered before Fote. Significantly, these associations with anti-oestrogens enabled the IC50 values of Fote to be reduced by up to 80%. Globally, TMX and 4OH TMX had similar synergistic effects. TMX and 4OH TMX had a modest influence on Fote cytotoxic effects against CAL 7 ER-negative cells. These data may be useful for optimal planning of future clinical trials for malignant melanoma using anti-oestrogens and nitrosoureas.