Computerized quantitation of synergism and antagonism of taxol, topotecan, and cisplatin against human teratocarcinoma cell growth: a rational approach to clinical protocol design.

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BACKGROUND: Cisplatin-based induction chemotherapy may achieve a complete response (i.e., no sign of tumor following treatment) in 70%-80% of patients with germ cell tumors. However, only a minority of patients in whom the frontline regimens fail are cured with the salvage regimens. PURPOSE: The aim of these studies was to identify new agents or new regimens for the treatment of germ cell tumors by carrying out quantitative assessment in vitro of two promising new antitumor agents (paclitaxel [Taxol] and topotecan) and three more established agents (cisplatin, vincristine, and etoposide). These agents were used singly or in two- and three-drug combinations and were selected because they represent five distinct categories of antineoplastic mechanisms. METHODS: The combination index-isobologram method, which is based on the median-effect principle developed by Chou and Talalay, was used for computerized data analysis. This method was selected because it takes into account both the potencies of each drug and combinations of these drugs and the shapes of their dose-effect curves. RESULTS: Synergism against the growth of teratocarcinoma cells resistant to cisplatin (833K/64CP10 cells) was greater than against the growth of parent 833K cells. The degrees of synergism were in the following order: cisplatin + topotecan > or = paclitaxel + cisplatin + topotecan > paclitaxel + topotecan > or = paclitaxel + etoposide > paclitaxel + cisplatin + etoposide > paclitaxel + cisplatin. All other combinations showed nearly additive effects or moderate antagonism. The degrees of antagonism were as follows: cisplatin + etoposide > or = paclitaxel + vincristine > paclitaxel + cisplatin + vincristine > cisplatin + vincristine. The combination of paclitaxel and cisplatin was synergistic against 833K/64CP10 cells and moderately antagonistic against 833K cells. Since the combination of paclitaxel, cisplatin, and topotecan and the two-component combinations of these drugs (cisplatin + topotecan and paclitaxel + topotecan) showed synergism stronger than that of other combinations, these three drugs were selected for illustrating detailed data analysis, using a computer software program developed in this institute. CONCLUSIONS AND IMPLICATIONS: Our findings suggest that, as a result of synergy, the doses of
these agents needed to achieve an antitumor effect may be reduced by twofold to eightfold when these agents are given in combination. The present quantitative data analyses for synergism or antagonism provide a basis for a rational design of clinical protocols for combination chemotherapy in patients with advanced germ cell tumors.