

Appearance of Aberrant Mitosis in Murine Leukemia Cells upon Combined Treatment with Low Concentrations of Cisplatin and Teniposide

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The combination of *cis*-diamminedichloroplatinum (II) (DDP, cisplatin) and topoisomerase II inhibitor teniposide (VM-26) has been shown to exert a synergistic effect in the clinical treatment of cancer. In this study, the combined effect of DDP and VM-26 on the growth and induction of apoptosis in synchronized murine erythroleukemia (MEL) cells, treated at the beginning or in the middle of S-phase of cell cycle, was examined. MEL cells, clone F4 N, were synchronized by a double thymidine block leading to accumulation of 70% of cells at the G₁/S boundary. The growth-inhibitory effect of DDP and VM-26 applied alone were stronger in the middle of the S-phase than at the beginning. Morphological analysis showed that the majority of the cells revealed typical signs of apoptosis: nuclei fragmentation and appearance of apoptotic bodies. The combination of both agents at low concentrations had a synergistic effect on cytotoxicity. At higher concentrations the effect was additive. The remainder of the cells were characterized by unbalanced growth, aberrant mitosis and appearance of multinucleated cells. These processes led to delayed cell death. The appearance of aberrant mitosis was more expressed after treatment in the middle of the S-phase. It is likely that as a result of the combined action of cisplatin and VM-26, cells become supersensitive to the ability of topoisomerase II inhibitor to influence mitosis, and this increased sensitivity may contribute to the observed synergism.