Late-Breaking Abstract Conference

BVDU co-treatment sensitizes for chemotherapy-induced apoptosis and inhibits chemoresistance

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During the implementation of a long-term screening program for inhibitors of induced chemoresistance, the pyrimidine nucleoside analog (E)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) was the only substance of clinical relevance we identified. BVDU co-treatment enhanced apoptosis and inhibited chemoresistance. This might have been due to the following effects of BVDU: 1) Inhibition of survival pathways and DNA repair associated enzymes. BVDU co-treatment might have promoted apoptosis by blocking the anti-apoptotic survival pathways that involve the oncogenes STAT3, JUN-D, and DDX1. Moreover, BVDU reduced the expression of the repair enzymes UBE2N and APEX to about 30% of control. 2) Induction of DT-diaphorase activity, an activator of quinone-type anticancer drugs. 3) Suppression of chemotherapy-induced *Mdr1* or *Dhfr* gene amplification, 4) Reduced expression of ATP-generating enzymes in the recovery phase, when the cytostatic drug was omitted, but BVDU still present. The expression of nine genes increased, and that of five genes decreased. Gene products linked to microfilament formation, differentiation, and signal transduction were affected, too.

In rats, co-treatment of doxorubicin (DOX), glufosfamide, or cisplatin with BVDU inhibited the growth of implanted AH13r sarcomas as well as that of dimethylbenzanthrazene (DMBA)-induced and DOX-treated fibrosarcomas and mammary adenocarcinomas. In these experiments, treatment with DOX for 50 days caused *Mdr1* gene amplification and overexpression in DMBA-induced rat tumors. Co-treatment with BVDU inhibited this cytostatic drug-induced effect. In the experiments with AH13r sarcomas treated for only 20 days, no gene amplification could be observed. In *in vivo* experiments, BVDU reduced the non-specific toxicity of DOX, and to a lesser extent that of cisplatin and glufosfamide.

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