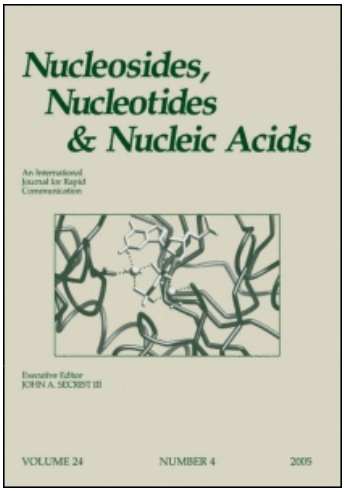

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Cell Specific Cytotoxicity and Structure-Activity Relationship of Lipophilic 1-B-D-Arabinofuranosylcytosine (Ara-C) Derivatives

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CELL SPECIFIC CYTOTOXICITY AND STRUCTURE-ACTIVITY RELATIONSHIP OF LIPOPHILIC 1-B-D-ARABINOFURANOSYLCYTOSINE (ARA-C) DERIVATIVES

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ABSTRACT: Lipophilic derivatives of ara-C were developed with the aim to improve drug penetration and retention in solid tumors. Ara-C was esterified at the 5'-position with fatty acids (16-22 C-atoms, 0-3 double bonds). The derivatives were inactive in cell lines with various forms of ara-C and 2',2'-difluorodeoxycytidine (dFdC, gemcitabine) resistance, including deoxycytidine kinase (dCK) deficiency. The activity in the parent cell lines correlated negatively with chain length and positively with double bonds.

Ara-C is a cytidine analog which is dependent on deoxycytidine kinase (dCK) phosphorylation for its activity. Ara-C is a widely used drug for treatment of hematological malignancies, but is inactive against solid tumors. This may be due to poor uptake and/or retention in the tumors[1]. Ara-C has, however, activity as intraperitoneal treatment of ovarian cancer, possibly due to prolonged exposure. Therefore fatty acid chains with varying lengths (16-22 C-atoms) and 0-3 double bonds were attached to the 5'-position of the sugar moiety of ara-C and 11 derivatives were tested in 4 pairs (parent-resistant) of cell lines with acquired resistance to either ara-C or gemcitabine (dFdC).

EXPERIMENTAL: Leukemic cell lines; murine L1210 and rat BCLO and their ara-C resistant (dCK deficient) variants L4A6 and BaraC, resp, were tested for cytotoxicity by cell counting[2]. A2780 ovarian cancer, its dFdC-resistant variant (AG6000; dCK deficient), C26-A murine colon cancer, and its dFdC-resistant variant C26-G, unknown resistance, normal dCK) were tested using the sulforhodamide test[3,4]. Deoxycytidine deaminase (dCDA) was partially purified using stepwise ammoniumsulphate precipitation.

RESULTS AND DISCUSSION: From the parent cell lines L1210 cells were the most sensitive to the derivatives (0.004-1.3 μM), followed by A2780 (0.012-27.4 μM) and BCLO (0.17-26.5 μM) cells, C26-A cells were least sensitive (1.6-68 μM). All compounds were less active than ara-C and dFdC, indicating an incomplete or delayed conversion to the parent drug. Cross-resistant (dependent on chain length and double bonds) with ara-C was observed in all cell lines, but most pronounced in AG6000 (all IC50 values above the maximal usable 100 μM), followed by L4A6 (100-100000 fold cross-resistance) and Bara-C (6-667 fold) and only moderately in C26-G (0.5-8.2 fold), indicating a dependence on dCK for activation. In parent cells a clear structure-activity relationship (SAR) was observed: IC50 values increased 8-fold with chain length, while saturated compounds were 3-9-fold less sensitive than unsaturated compounds. Compounds with a chain length of 18 or 20 C-atoms showed a relatively better activity (3-5 and about 30-fold, resp) at a short exposure than ara-C, indicating some sort of retention or slow release of ara-C in the cell, possibly related to decreased deamination. P-4055, an 18-C compound was tested with partially purified dCDA but no deamination to ara-U was observed. P-4055 was similarly active as ara-C *in vivo* against s.c. C26-A and C26-G tumors, when administered i.p. daily 5x at its maximal tolerated dose. C26-G was slightly less sensitive than C26-A. In conclusion; cytotoxicity of these ara-C analogs showed a clear SAR with chain length; this apparently influences retention in tumor cells, which may favor development as a slow release drug eventually for local treatment.

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