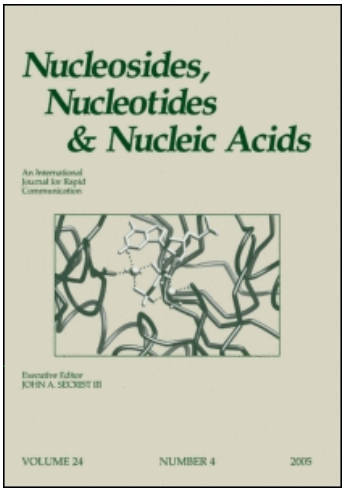

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Antiproliferative Activity and Mechanism of Action of Fatty Acid Derivatives of Arabinosylcytosine (ara-C) in Leukemia and Solid Tumor Cell Lines

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ABSTRACT

Resistance to, the hydrophilic drug ara-C, might be meditated by decreased membrane transport. Lipophillic prodrugs were synthesized to facilitate uptake. These compounds were equally active as ara-C, while the compounds with the shortest fatty-acid group and highest number of double bonds were the more active. These compounds also show a better retention profile, their effect is retained longer than for ara-C.

Key Words: ara-C; Arabinosylcytosine; Fatty acid derivatives; Antiproliferative activity; Leukemia; Solid tumor.

INTRODUCTION

The anticancer drug ara-C is a deoxycytidine (dCyd) analog, which is the major drug in the treatment of acute leukemia.[1] Altered transport over the cell membrane is a mechanism

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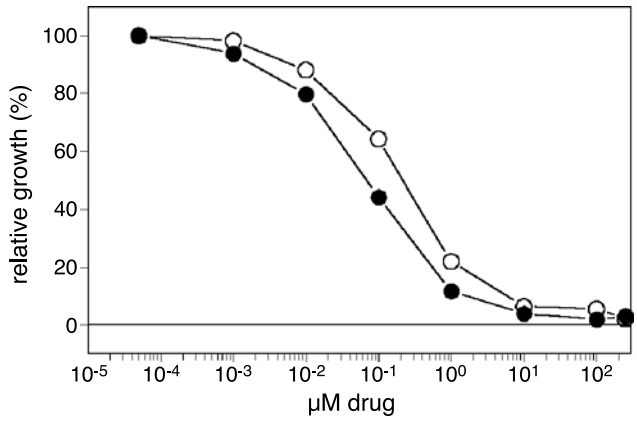

Figure 1. Representative growth inhibition curves of the BCLO cells exposed for 72 hr to ara-C (-●-) or to the fatty acid derivative CP-4055 (-○-). SE are within the size of the symbol.

of drug resistance.[2] To facilitate ara-C uptake and prolong retention in the cell, lipophillic pro-drugs were synthesized. Fatty acid groups with a varying acyl chain length and number of double bonds were esterfied at the 5′ position on the sugar moiety of ara-C.

MATERIALS AND METHODS

The compounds were tested in various leukemia and solid tumor cells of murine, rat and human origin both parental and drug resistant. Growth inhibition in suspension growing leukemia cells was determined by a cell counting method and in the monolayer solid tumor cells the SRB assay was performed.[3]

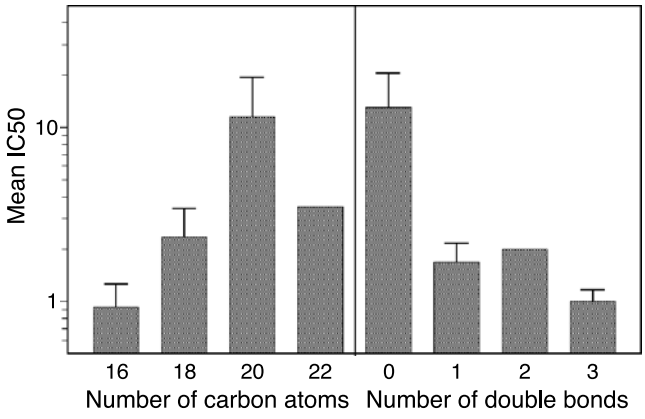

Figure 2. Relationship between chain length, number of double bonds and efficacy of ara-C derivatives in various cell lines, expressed as mean IC50 value in nM ± SEM.

Table 1. Retention of growth inhibition by ara-C analogs in murine colon cancer cells (C26-A) and its gemcitabine resistant variant C-26G.

	Ratio IC50s of 4/72 hr	
Compound	C26-A	C26-G
Ara-C	180	453
CP-4055	78.4	92.5
CP-4057	67.2	92.5
CP-4098	6.3	13.9

The ratios of the IC50s were calculated for each separate experiment; means were calculated from these values.

RESULTS

The fatty acid derivatives were at least equally active as ara-C in the cell lines tested (Fig. 1 and data not shown). Derivatives with the shortest fatty-acid group and highest number of double bonds were the more active (Fig. 2). Several of the more active compounds were chosen for further study. We exposed cells for a 4 hr period to the drugs followed by a drug-free period of 68 hr, or cells were exposed for the full 72 hr. This gives information on the retention of the effects. The ratio IC50 for 4/72 hr was highest for ara-C confirming that a long exposure is essential for this compound. The other compounds showed a much lower ratio indicating a retained effect in the cell (Table 1).

DISCUSSION

The tested compounds were active in both leukemia and solid tumor cells. A clear structure activity relationship was found, in which the shorter chains were more active than the longer chains. Because of the lipophilicity the drugs can bypass a potential transport problem,[4] they are able to enter transport deficient cells and will bypass inhibition of equiliberative transporter by dipyridamol. In addition, their special structure not only allows rapid nucleoside transporter independent uptake, but also a longer retention of active metabolites (Ara-CTP) or prolonged effect (inhibition of DNA synthesis). Considering the lower ratio for the 4/74 hr exposure, it might be possible that the compounds are retained in some not yet elucidated intracellular compartment. In conclusion, the fatty acid derivatives seem to be promising drugs, as was previously shown in xenografts.[4] Since CP-4055 was found highly active in vitro and had a striking activity in solid tumor xenografts in contrast to ara-C, this drug is selected for clinicalevaluation.

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