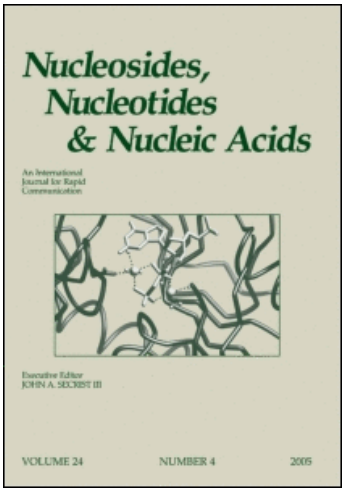

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5-Hydroxymethyl-2'-Deoxyuridine: Studies of Antileukemic Properties in Vitro and in Vivo

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5-HYDROXYMETHYL-2´-DEOXYURIDINE: STUDIES OF ANTILEUKEMIC PROPERTIES IN VITRO AND IN VIVO.

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Abstract - 5-Hydroxymethyl-2´-deoxyuridine (5HmdUrd) prolonged the survival of mice carrying leukemia L1210 in a dose-dependent manner. Furthermore, a dose-dependent synergism/antagonism was observed when human leukemia cells were exposed simultaneously to Ara-C and 5HmdUrd in vitro.

INTRODUCTION

5-Hydroxymethyl-2´-deoxyuridine (5HmdUrd) is an "off-the-shelf" thymidine analogue having biological activity against bacteria and various mammalian cells in culture. We became interested in the compound because it has considerable activity against different types of human leukemia cells in vitro[1]. Investigation of the compound in our laboratories has proceeded along two lines: (i) clarifying the mode of action as well as studying the possible interactions of 5HmdUrd in vitro, and (ii) assessing the properties of 5HmdUrd in mice using leukemia L1210 as the target. The current results are reported in this communication.

RESULTS

In vitro studies

5HmdUrd had a dose-dependent toxicity against a human acute promyelocytic leukemia cell line (TABLE 1). 5HmdUrd (10^{-5} and 10^{-4} M) significantly potentiated the toxicity of Ara-C (10^{-7} and 10^{-6} M). On the other hand, a smaller Ara-C concentration (10^{-8} M) effectively reduced the toxicity of 5HmdUrd, as shown in TABLE 1.

TABLE 1. Effects of 5HmdUrd and Ara-C on the growth of human leukemia cells (HL-60).

5HmdUrd (M)	Living cells per microliter: Ara-C concentration None	10^{-8} M	10^{-7} M	10^{-6} M
None	94 (21)	88 (9)	91 (8)	39 (9)
10^{-5}	93 (15)	86 (26)	56 (3)	9 (6)
10^{-4}	12 (3)	33 (9)	6 (2)	4 (2)

[a]Cells were suspended at a density of 10^5/ml and grown for 3 days in microplate cultures. Living cells were counted hemocytometrically with trypan blue dye exclusion. Each point represents the mean (SD) of four determinations.

TABLE 2. Effect of different concentrations of 5HmdUrd on the survival time of mice with L1210 leukemia.

Dose[a] (mg/kg)	Mean survival (days ± SD)	N
0	12.0 ± 1.2	5
5	16.8 ± 1.0	4
50	29.0 ± 16.0	4

[a]Given twice a day for five days.

In vivo studies

The plasma half-life of 5HmdUrd in mice was only about 0.5 hr, when the compound was given as an i.p. injection. We also demonstrated that 5HmdUrd prolonged the survival of DBA/2 mice carrying L1210 leukemia, as shown in TABLE 2.

DISCUSSION

The present results demonstrated that 5HmdUrd can be used as an antileukemic agent in vivo. Furthermore, we demonstrated the potential

of the compound against human leukemic cells in vitro. It remains to be clarified whether the compound has any activity against human leukemia in vivo.

The synergism of Ara-C and 5HmdUrd was expected on the basis of our previous studies, where we demonstrated that 5HmdUrd potentiated (several-fold) the incorporation of radioactive deoxycytidine into human HL-60 cells[2]. It is possible that 5HmdUrd causes deoxycytidylate starvation, similar to that caused by thymidine, and thus increases the incorporation of Ara-C via the salvage pathway of deoxycytidine. The mechanism of the antagonism between 5HmdUrd and Ara-C noted with a low Ara-C concentration remains to be clarified.

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