Inhibition of Tumor Growth with Ultralow Doses of Doxorubicin under Experimental Conditions

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Antitumor activity of ultralow doses of cytostatic doxorubicin was studied on BDF_1 mice with Lewis lung carcinoma. The preparation was injected intraperitoneally in single doses of 10^{-5}, 10^{-10}, 10^{-15}, and 10^{-20} M on the next day after tumor inoculation. The effect of ultralow doses was compared with that of a standard therapeutic dose of doxorubicin (8 mg/kg, 1.4×10^{-3} M). Doxorubicin in ultralow doses produced an antitumor effect comparable with that induced by the preparation in standard doses. On day 12 after administration of doxorubicin in ultralow and standard doses, tumor size in mice did not exceed 20% of the control level.

Key Words: *antitumor activity; doxorubicin; ultralow doses*

Low selectivity of modern antitumor preparations (damage to not only tumor, but also normal tissues) is the main factor limiting their use for the treatment of tumors. Ample recent data on high biologically activity of various physical and chemical agents in ultralow doses (ULD) provide the basis for the development of new approaches to the use of standard medicines [1-3].

In oncology this approach implies refusal of the concept of "high-dose therapy" and the development of new methods for treatment with ULD of cytostatics inhibiting tumor growth and producing no toxic side effects.

The antitumor preparation N-nitroso-N-methylurea in ULD of 10^{-17} mol/kg produces chromosome aberrations in leukemia L-1210 and Ehrlich tumor cells and prolongs the lifespan of tumor-bearing animals by 40% compared to the control [4-6].

Here we studied the biological effectiveness of ULD of routine cytostatic doxorubicin widely used in clinical practice.

MATERIALS AND METHODS

Experiments were performed on BDF_1 mice with Lewis lung carcinoma. The animals weighted 10-20 g and were obtained from the Stolbovaya nursery.

Doxorubicin was administered in doses of 10^{-5}, 10^{-10}, 10^{-15}, and 10^{-20} M. The effect of ULD was compared with the effect of a standard therapeutic dose (8 mg/kg, 1.4×10^{-3} M).

Doxorubicin (0.2 ml in water) was injected intraperitoneally on the next day after tumor inoculation. The solutions were prepared by multiple serial dilutions and mixing. The concentration of the initial solution corresponded to the standard therapeutic dose.

The antitumor effect was evaluated by changes in tumor size and lifespan of mice (in percents of the control).

The results were analyzed using Statistica software.

RESULTS

The maximum tumor size and the mean lifespan in control mice were 6.6±0.4 g and 28.5±2.5 days, respectively, which is consistent with published data on the development of Lewis lung carcinoma.

Doxorubicin in the standard therapeutic dose markedly inhibited tumor growth. The inhibitory effect was most pronounced on day 12 after doxorubicin administration. In this period tumor size in doxorubicin-treated mice did not exceed 17% of the control level (Fig. 1).

Doxorubicin in all ULD retained the ability to inhibit tumor growth (Fig. 1). The inhibition of tumor growth produced by doxorubicin in ULD and standard therapeutic dose was characterized by the same kinetics.

The effect of doxorubicin in various doses was most pronounced on day 12 after treatment. At later terms tumor growth was partially restored. It should be emphasized that 25 days after administration of doxorubicin in the standard dose and ULD, tumor size was about 2-fold lower than in the control (Fig. 1).

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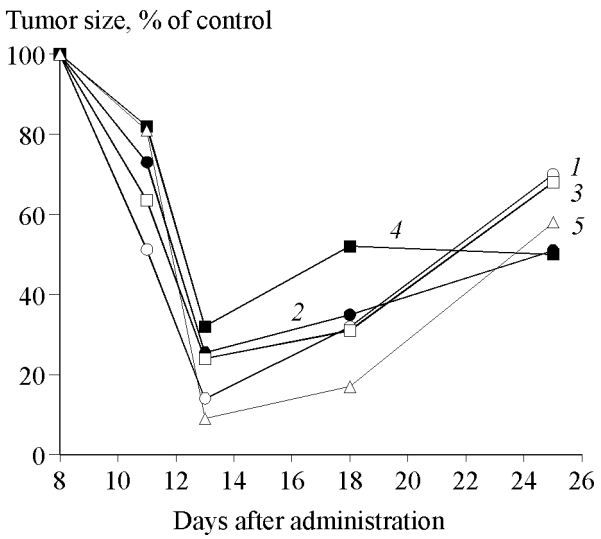

Fig. 1. Effects of doxorubicin in various doses on growth kinetics of Lewis lung carcinoma: standard dose (1.4×10^{-3} M, *1*), 10^{-5} (*2*), 10^{-10} (*3*), 10^{-15} (*4*), and 10^{-20} M (*5*).

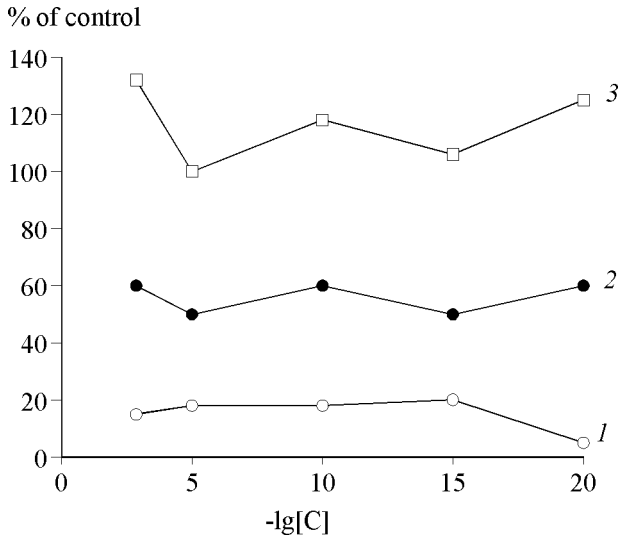

Fig. 2. Dose dependence of the antitumor effect of doxorubicin in mice with Lewis lung carcinoma. Abscissa: molar concentration of the preparation. Relative tumor size on days 12 (*1*) and 25 (*25*) after administration of the preparation; relative lifespan (*3*).

The dose-effect curves show that ULD and standard dose of doxorubicin produced similar tumor-inhibiting effects (Fig. 2). On day 12 after administration of ULD (10^{-5}, 10^{-10}, and 10^{-15} M) and standard dose of doxorubicin, tumor size in mice did not exceed 20% of the control value. In animals receiving 10^{-20} M doxorubicin tumor size was less than 5% of the control (Fig. 2).

On day 25 the differences between the effects of doxorubicin in ULD and standard dose were insignificant. Tumor size in doxorubicin-treated mice did not exceed 50-60% of the control independently on the dose of this preparation (Fig. 2).

The lifespan of mice receiving 10^{-10} and 10^{-20} M doxorubicin was 117 and 128% of the control, respectively. Doxorubicin in the standard therapeutic dose more significantly increased this parameter (133% of the control). These results show that doxorubicin in ULD increased the lifespan of mice with Lewis lung carcinoma.

Our findings suggest that doxorubicin in ULD inhibited the growth of Lewis lung carcinoma, an experimental tumor low sensitive to most antitumor preparations.

The directionality of biological effects depends on the nature of agents, value of ULD, and type of tumors. Therefore, antitumor activity of ULD of cytostatics with different mechanisms of action should be studied on various models of tumor in animals.

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