Modification of Chemotherapeutic Activity in Adriablastine with the Synthetic Antioxidant in Low Doses

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Synthetic antioxidant potassium phenosan in ultralow doses administrated in combination with antitumor antibiotic adriamycin in a therapeutic dose (8 mg/kg) markedly prolonged the mean life span of tumor-bearing animals compared to adriamycin monotherapy. This effect depended on the dose of antioxidant and was maximum at phenosan concentrations of 10^{-17} and 10^{-15} M. Potassium phenosan in these concentrations not only increased the mean life span, but also determined survival of 10-20% animals (as differentiated from adriamycin monotherapy).

Key Words: *ultralow doses; combination chemotherapy; synthetic antioxidant*

Our previous studies showed that various bioactive substances are effective not only in physiological (10^{-3}-10^{-6} M), but also in ultralow concentrations (10^{-12}-10^{-18} M) [1,3,4]. Synthetic antioxidant potassium phenosan (PPh) acts as a potent activator of protein kinase C. It should be emphasized that PPh is equally effective in concentrations of 10^{-4} and 10^{-16} M [3,4]. There is evidence that protein kinase C serves as a target for antitumor agents [7]. This led as to an assumption that antioxidants in ultralow doses can modulate the effect of classical antitumor drugs.

MATERIALS AND METHODS

Experiments were performed on 480 C57Bl×DBA_2/F_1 mice obtained from Stolbovaya nursery. Ascitic P-388 leukemia cells were inoculated intraperitoneally on day 7 of tumor growth (10^6 cells, 0.2 ml). Adriablastin (AB) was injected intraperitoneally in a single dose of 8 mg/kg on day 1, 3, or 5 after tumor inoculation [2]. Experimental mice (10 animals per group) received combination therapy with AB and PPh. The antioxidant in doses of 10^{-17}, 10^{-15}, 10^{-12}, 10^{-11}, 10^{-10}, 10^{-9}, or 10^{-7} M was injected 1 h before AB administration. Control mice (10 animals per group) received AB alone.

The effect of preparations on tumor growth was evaluated by the relative increase in the mean life span (MLS) of animals:

$$[(MLS_T\text{-}MLS_U)/MLS_U]\times 100,$$

where MLS_T and MLS_U are MLS of treated (AB or AB+PPh) and untreated mice, respectively.

The results were processed statistically using Student's *t* test.

RESULTS

Single treatment with the standard medicine and adjuvant adequately reflects the efficiency of this adjuvant during combination chemotherapy of animals with tumors. In animal experiments AB can be used in single doses of 5-15 mg/kg body weight. Our previous experiments showed that a concentration of 8 mg/kg is optimum for these studies [2]. To determine the optimum term of treatment with AB, we compared MLS of animals receiving AB on days 1, 3, and 5 after tumor inoculation (Table 1). AB administered at various terms after inoculation of tumor cells increased MLS of animals, but the most pronounced effect was observed after administration of AB on day 3 after inoculation (Table 1). In further experiments with combination therapy, AB was administered on day 3 after tumor inoculation. AB increased MLS of mice by 44±4% compared to untreated animals. During combination therapy PPh in various doses modulated the effect of AB. In some concentrations PPh considerably improved the positive effect of AB (Fig. 1). During combination chemotherapy 10% mice survived, while all animals receiving AB monotherapy died. Moreover, MLS of mice with tumors receiving combination therapy surpassed that of animals treated with AB alone. For instance, combination treatment with AB and PPh in ultralow doses (10^{-17} M) determined survival of 10% mice and increased MLS of tumor-bea-

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0007-4888/03/supp-0052$25.00

TABLE 1. MLS of C57Bl×DBA_2/F_1 Mice Receiving AB in a Dose of 8 mg/kg at Various Periods after Inoculation of Leukemia P-388 Cells (*M*±*m*, *n*=10)

Parameter	Control	Period, days		
		1	3	5
MLS, days	13.0±0.2	18.2±0.3	19.0±0.5	17.2±0.3
Increase in MLS, days	—	5.2±0.3	6.0±0.5	4.2±0.3
% of control	—	40±5	47±6	32±7

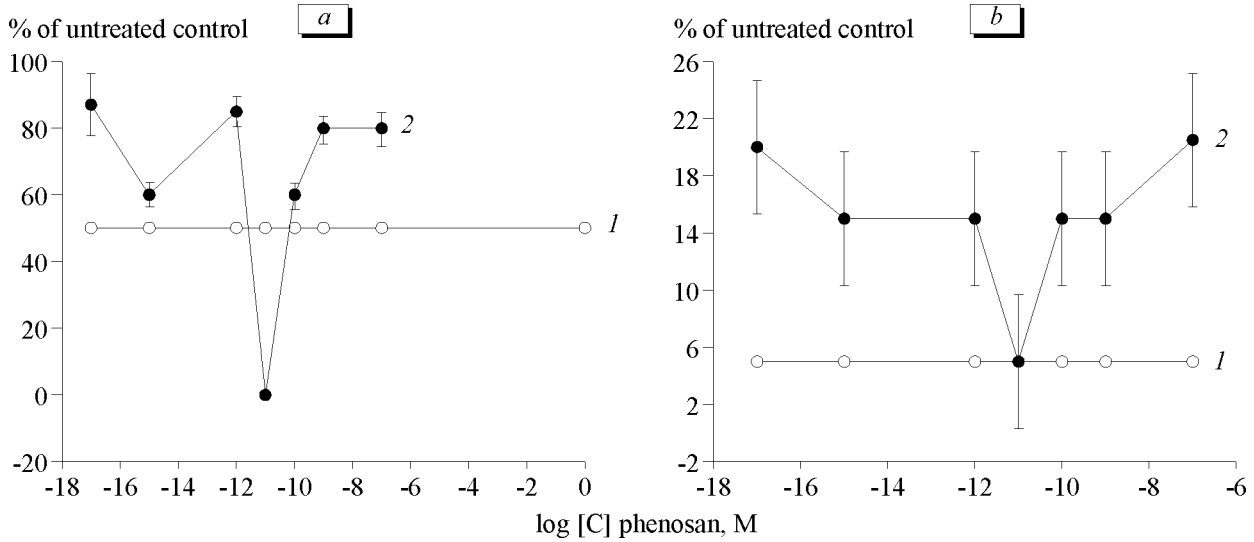

Fig. 1. Dependence of the average life span (*a*) and survival (*b*) of tumor-bearing animals injected with adriablastin on day 3 after tumor inoculation (*1*) and receiving combination therapy with adriablastin and phenosan (*2*) on the dose of potassium phenosan.

ring animals by 83%. It is interesting that the survival rate and MLS were similar in animals receiving PPh in concentrations of 10^{-7}, 10^{-9}, 10^{-12}, and 10^{-17} M. The dose-response relationships were also similar. PPh in ultralow and relatively high concentrations (10^{-12}-10^{-17} and 10^{-10}-10^{-7} M, respectively) produced positive effects on MLS and survival rate. However, PPh in a dose of 10^{-11} M did not potentiate the effect of AB, but even completely abolished it: zero survival and MLS did not differ from that in untreated control. By the type and other characteristics, these dose-response relationships correspond to curves describing the effect of chemical substances in ultralow concentrations [5,6].

Our results suggest that PPh in ultralow doses modulates the effect of antitumor agents. The increase in the life span by 20-30% and improvement in survival (even minimal) give good grounds to recommend this nontoxic antioxidant for introduction in clinical practice.

The work was supported by Moscow Government (grant No. 225/97-ONK-2-TEMN).

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