ANTILEUKEMIC ACTIVITY OF L-LYSINE-α-OXIDASE FROM Trichoderma SP. IN EXPERIMENTAL CHEMOTHERAPY

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An urgent problem in modern experimental chemotherapy is the search for and study of antitumor agents isolated from various natural sources [12]. One promising enzyme of this class is L-lysine-α-oxidase, which was first isolated from the fungus Trichoderma and obtained in a homogeneous state (independently) in two laboratories: by Soda (Japan) [7] and by Berezov (USSR) [3]. L-lysine-α-oxidase is superior to other bacterial enzyme preparations with established antitumor activity in a number of catalytic and biological properties: in particular, it possesses high catalytic activity, specificity of action, and high affinity for the substrate (a low value of K_m); moreover, according to available data [1, 8], in experiments in vivo in which L-lysine-α-oxidase was administered in minimal concentration to animals with leukemia it exhibited stable and high antitumor activity.

In previous investigations [4, 6] the writers demonstrated the cytostatic activity of L-lysine-α-oxidase obtained from a Soviet producer strain of Trichoderma sp., and also attempted to discover certain molecular mechanisms of its antiproliferative action in experiments in vitro.

The aim of this investigation was to assess the chemotherapeutic effect of L-lysine-α-oxidase from Trichoderma sp. against two strains of transplantable leukemia: L1210 and P388.

EXPERIMENTAL METHOD

A homogeneous (by gel-electrophoresis and ultracentrifugation) preparation of the enzyme L-lysine-α-oxidase from Trichoderma sp. with specific activity of 29 U/mg, obtained by methods developed in the Department of Biochemistry of the Patrice Lumumba Peoples' Friendship University and the "Ferment" Scientific-Industrial Association (Vilnius), was used.

The antileukemic activity of the enzyme preparation on a test model of P388 was determined by the method used in the All-Union Oncologic Scientific Center, Academy of Medical Sciences of the USSR [5], and on a test model of L1210 by a similar method. Male BDF_1 mice weighing 20-21 g were used, Each animal was given 10^6 cells of lymphatic leukemia L1210 and P388 by intraperitoneal implantation.

The test enzyme preparation was dissolved in 0.9% NaCl immediately before use and injected intraperitoneally, the first time 24 h after inoculation of leukemia, in different doses and by different schedules as indicated in Table 1. Each experimental group consisted of three animals and each control group of six mice. Table 1 gives the end results of five experiments on the P388 test model and two experiments on the L1210 test model.

The criterion of minimal therapeutic activity, namely an increase of 25% in the mean length of survival (MLS) of the experimental animals compared with the controls, was adopted for both test models.

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TABLE 1. Antileukemic Activity of L-Lysine-α-Oxidase from Trichoderma sp. against Transplantable Leukemias L1210 and P388

Strain	Dose of L-lysine-α-oxidase, U/kg		Number of injections	Interval between injections, days	Increase in MLS compared with control, %
	sessional	total			
L1210	35	35	1	—	5
L1210	35	70	2	4	4
L1210	35	175	5	2	36
L1210	70	70	1	—	17
L1210	70	140	2	4	16
L1210	70	350	5	1	18
P388	17,5	35	2	4	10
P388	17,5	87,5	5	2	12
P388	35	70	2	4	27
P388	35	175	5	1	54
P388	70	140	2	4	25
P388	70	350	5	1	28
P388	140	140	1	—	9
P388	140	700	5	1	22

Legend. Experimental results given as arithmetic mean value of five determinations ± standard deviation; differences between values significant at the $p \leq 0.05$ level. MLS) Mean length of survival.

EXPERIMENTAL RESULTS

The therapeutic effect of L-lysine-α-oxidase on mice with lymphatic leukemia L1210 (an increase in MLS by 36%) was found with only one dose schedule: five injections each of 35 U/kg. In Soda's experiments [8] on the same test model a similar therapeutic result was achieved: an increase of 34-48% in MLS, but after five injections each of 70 U/kg.

The data in Table 1 also demonstrate the very narrow therapeutic interval of L-lysine-α-oxidase on the L-1210 test model. Conversely, on the P388 test model this enzyme exhibits its antileukemic activity over a wide range of doses, evidence of a strong therapeutic effect.

Analysis of the data so far obtained in experimental oncology shows that high activity of substances for the P388 test model is combined as a rule with a high probability of manifestation of specific activity on other experimental systems and in clinical factors [2].

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