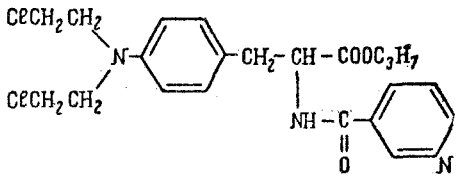
EXPERIMENTAL DATA CONCERNING THE ISOPROPYL ESTER OF αN-NICOTINOYL-SARCOLYSIN

I. G. Spasskaya

Laboratory of Experimental Chemotherapy (Head – Corresponding Member AMN S SSR Prof. L. F. Larionov), Institute of Experimental and Clinical Oncology (Dir. – Active Member AMN SSSR N. N. Blokhin), AMN SSSR, Moscow
(Presented by Active Member AMN SSSR A. D. Timofeevskii)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 51, No. 2, pp. 92-95, February, 1961
Original article submitted February 18, 1960

The idea on which was based the production of preparations of the type of the complex alkylating metabolites has been described previously [1, 2]. In some of the preparations which have been described and studied the complex carrier of the cytotoxic (chloroethylamine) group took the form of dipeptides. In the present preparation the carrier of the cytotoxic group is a compound of an amino acid (phenylalanine) and a vitamin (nicotinic acid).

The isopropyl ester of αN-nicotinoyl-sarcolysin has the following structure:



The compound was synthesized by E. N. Shkodinskaya, O. S. Vasina and A. Ya. Berlin in the chemical division of the Institute of Experimental and Clinical Oncology of the Academy of Medical Sciences of the USSR. In the present article we describe the results of an experimental investigation of this preparation.

EXPERIMENTAL METHOD

In order to study the antitimor action of the preparation different strains of transplantable tumors were used: in rats – spindle-cell sarcoma 45 and ascites hematoma (French strain); and in mice – Ehrlich's tumor (ascites and solid forms), carcinoma of the mammary gland (strains RMZh and MAP), carcinoma of the forestomach (OZh-5), sarcoma 298 and Crocker's sarcoma 180 (the last in ascites and solid forms).

In the case of the solid tumors administration of the preparations began when they reached a weight of 0.5-1.0 g in rats and 0.1-0.2 g in mice, and in the case of ascites tumors 24 hours after transplantation.

Since the preparation is insoluble in water it was administered to the animals in the form of a suspension in a 1-2% starch paste. The oral and intraperitoneal methods of administration were used. In solid tumors transplanted subcutaneously the preparation was given intraperitoneally or orally, and in ascites forms of the tumors it was always given intraperitoneally. In therapeutic experiments the preparation was given daily for 15-20 days.

The results of the experiments were evaluated as a percentage of inhibition and by rate of growth. In the experiments with ascites strains consideration was paid to the volume of ascites fluid, and the percentage of inhibition was calculated from the difference in the volume of ascites fluid in the experimental and control animals. The results were treated statistically by Student's method.

The study of the antitumor action of the preparation was carried out on 80 rats and 350 mice. In determining the toxicity of the preparation, it was injected into animals as a single dose. The results of these experiments were evaluated by the percentage of animals which died in the course of 30 days.

EXPERIMENTAL RESULTS

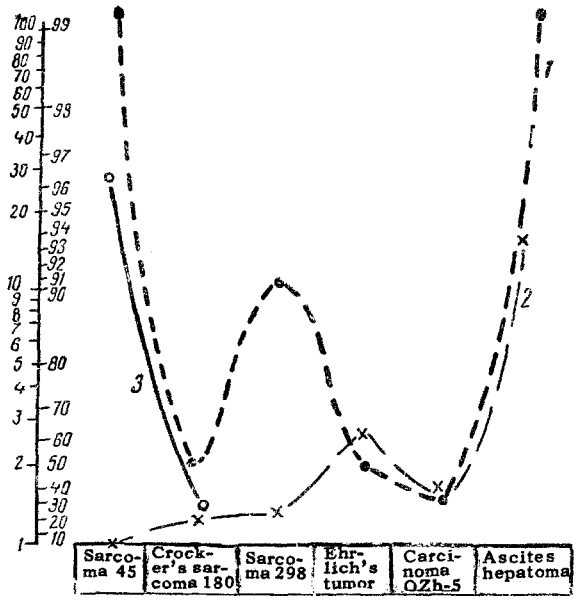
The toxicity of the preparation was first studied. The experiments showed that it possesses low toxicity: for instance, a dose of 1000 mg/kg, when injected once intraperitoneally, did not cause the death of rats and mice. Doses of 175-300 mg/kg, when administered daily for 15 days, were well tolerated by the animals.

The effect of the preparation on the blood was studied in a therapeutic experiment with Ehrlich's tumor. It was found that the white cell count in the peripheral blood remained normal when the preparation was given in a dose of 200 mg/kg daily for 15-20 days. A decrease in the weight of the spleen by one-third or one-half was, however, observed under these conditions. The results relating to the antitumor action of the preparation are given in the table.

The Action of the Isopropyl Ester of αN-Nicotinoyl-Sarcolysin

Strain of tumor	Dose (in mg/kg)	Mode of administration	Number of animals	Mean weight of tumor (in g)		Volume of ascites fluid (in ml)		Inhibition (in %)	Criterion of significance
				control	expt.	control	expt.		
Ascites hepatoma	200	Intraperitoneally	30	–	–	37	2.5	93	1
Mammary gland carcinoma (strain RMZh)	300	Orally	30	0.84	0.29	–	–	65.5	0.998
	200	Intraperitoneally	20	0.85	0.12	–	–	86	1
Strain MAP	300	Orally	40	2.9	2	–	–	31	0.9
Ehrlich's tumor (solid form)	200	Intraperitoneally	60	1.4	0.55	–	–	60 (44-72)	0.999
	300	Orally	30	1.2	0.65	–	–	46	0.999
Ehrlich's tumor (ascites form)	175	Intraperitoneally	20	–	–	2.8	1.6	43	0.95
Carcinoma of forestomach OZh-5	175	"	20	2.7	1.8	–	–	33	0.95
Sarcoma 298	200	Orally	48	2.7	2	–	–	25.5	
Crocker's sarcoma 180	175	Intraperitoneally	74	0.5	0.4	–	–	20	0.45
	300	Orally		0.6	0.57	–	–	0	
Ascites form	175	Intraperitoneally	30	–	–	2.3	1.7	26	
Sarcoma 45	200	"	50	37.5	40.7	–	–	0	

It will be seen from the table that the ascites hepatoma of rats was most sensitive to the preparation. For instance, in a dose of 200 mg/kg, when injected intraperitoneally for 13 days, the preparation inhibited growth of the ascites hepatoma of rats by 93%. In most of the treated animals traces of ascites fluid remained at the end of the experiment, but in control animals the volume of ascites reached 37 ml.



Spectra of antitumor action of the isopropyl ester of αN-nicotinoyl-sarcolysin and closely related compounds. 1) Sarcolysin; 2) isopropyl ester of αN-nicotinoyl-sarcolysin; 3) isopropyl ester of sarcolysin. Along the axis of abscissas are shown the forms of tumor; along the axis of ordinates (graduated in a logarithmic scale) are the indices of inhibition for each strain (on the left) and the corresponding percentages of inhibition (on the right).

The preparation also inhibited growth of the mammary gland tumor (strain RMZh) by 65-86% and of Ehrlich's tumor by 44-72%. The action of the preparation on the ascites and solid forms of Ehrlich's tumor was practically identical. The preparation had no action on sarcoma 45 of rats or on Crocker's sarcoma and sarcoma 298 in mice.

It was thus established that the preparation possesses some antitumor activity. Epithelial tumors, namely the ascites hepatoma of rats and carcinoma of the mammary gland (strain RMZh), were most sensitive to the preparation.

When the results of this investigation are compared with the data obtained in our laboratory by Sof'ina [3, 4] and Trusheikin [5] from studies of the action of sarcolysin and the isopropyl ester of sarcolysin, certain differences are found in the spectrum of action of these preparations. We show in the figure the spectrum of the antitumor action of these preparations (drawn from Larionov's scheme).

It can be seen from the figure that sarcolysin, and also the isopropyl ester of sarcolysin, have a strong inhibitory action on sarcoma 45 and sarcoma 298, whereas the isopropyl ester of αN-nicotinoyl-sarcolysin has no action whatsoever on these tumors. Both sarcolysin and the isopropyl ester of αN-nicotinoyl-sarcolysin, however, had equal effects on ascites hepatoma of rats, Ehrlich's tumor and carcinoma of the forestomach.

The analysis of our findings confirms Larionov's view [1] that, by changing the carrier of the functional group, preparations having a different spectrum of action can be created.

SUMMARY

The author studied the antiblastic effect of isopropyl ester of αN-nicotinoyl-sarcolysin on various strains of transplantable tumors. Epithelial tumors, namely rat ascitic hepatoma (French strain) and carcinoma of the mammary gland (CMG strain), proved to be the most sensitive to the preparation. The latter exerted no effect on rat sarcoma 45 or on Crocker's sarcoma 298 in mice. The strength and the range of the antiblastic effect of this preparation differed from that in similar compounds – sarcolysin and isopropyl ester of sarcolysin.

LITERATURE CITED

1. L. F. Larionov, Vestnik. Akad. Nauk SSSR, No. 12, 8 (1958).
2. L. F. Larionov, Vestnik. Akad. Nauk SSSR, No. 6, 25 (1959).
3. L. F. Larionov and Z. P. Sof'ina, Doklady Akad. Nauk SSSR 114, 5, 1070 (1957).
4. Z. P. Sof'ina, Transactions of the Second All-Union Oncological Conference [in Russian] (Leningrad, 1959) p. 773.
5. V. I. Trusheikina, Voprosy Onkol., No. 2, 222 (1956)