

RELATIONSHIP BETWEEN EFFECTIVENESS OF THE ANTITUMOR ACTION OF SARCOLYSIN AND THE LATENT PERIOD OF TUMOR DEVELOPMENT AFTER TRANSPLANTATION

T. N. Gavrilova, G. G. Ladnova, UDC 615.277.3.036.8+616-006-092.9-085.277.3-036.8
and M. F. Merkulov

After transplantation of a sarcoma induced by 3-methylcholanthrene into syngeneic mice the latent period of development of the tumor varied from 7 to 26 days. Sarcylisin was injected as a single dose at the moment of detection of the tumor by palpation. When the latent period of development of the tumor was 7-8 and 10-15 days, inhibition of its growth was accompanied by an increase in the survival period of the mice, and the increase was particularly great in the latter group. If the latent period of tumor development was 17-20 or 22-26 days, inhibition of tumor growth was not accompanied by an increase in the survival period of the mice.

KEY WORDS: latent periods; chemotherapy of tumors; sarcylisin.

The effectiveness of chemotherapy of tumors is largely dependent on the rate of growth of the neoplasm [3, 5]. The rate of growth of tumors, in turn, is determined by several factors, one of which is the latent period of development of the tumor.

No direct observations which could shed light on the relationship between the effectiveness of chemotherapy of tumors and latent period of their development have been reported. However, it has been shown that the rate of growth of transplantable tumors depends on the time of appearance of the tumor after transplantation [1]. The importance of the latent period of tumor development has also been emphasized during the study of correlation between the prognosis of the disease and the rate of growth of tumors in man [2, 4].

The object of this investigation was to study the effectiveness of the treatment of mice with tumors differing in the duration of their latent period of development after transplantation.

EXPERIMENTAL METHOD

Experiments were carried out on C57BL/6 mice weighing 20-22 g. The original tumor for the experiments was obtained in C57BL/6 mice by intramuscular injection of 0.5 mg of 3-methylcholanthrene dissolved in peach oil. The mouse was killed 3 months after injection of the carcinogen, when the volume of the tumor was 1 cm³, and the tumor was removed and freed from its capsule. After washing in cold physiological saline it was minced and pressed through a metal (tantalum) grid with holes 0.5 mm in diameter. The tissue mince was diluted with cold physiological saline in the ratio of 2:5. The cell suspension was carefully mixed and then allowed to stand in a refrigerator for 10 min. The supernatant containing single tumor cells was withdrawn by a pipet. The cell concentration in the suspension was determined in a Goryaev's chamber. The resulting cell suspension was injected subcutaneously in a dose of 10⁶ viable tumor cells per mouse. At the moment of appearance of a tumor, the animals were divided into experimental and control groups. The experimental mice were given sarcylisin in the maximal tolerated dose (15 mg/kg) intraperitoneally. Growth of the tumor was determined by measuring its diameter in three mutually perpendicular directions. The volume of the tumor was calculated by the equation for a sphere, using the mean diameter. The duration of the animals' survival was counted from the time of transplantation of the tumor until death of the animals.

Laboratory of Mechanisms of Action of Antitumor Preparations, Oncologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR N. A. Kraevskii.) Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 85, No. 2, pp. 197-199, February, 1978. Original article submitted June 25, 1977.

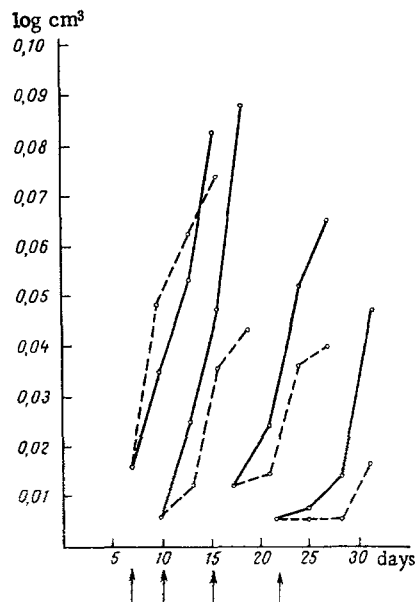


Fig. 1. Dynamics of growth of tumors as a function of time of their appearance after transplantation. Time of injection of sarcolysin indicated by arrows. Continuous line represents control mice; broken line experimental mice. Abscissa, time after transplantation of tumor (in days); ordinate, mean volume of tumor (in $\log \text{ cm}^3$).

TABLE 1. Effectiveness of Treatment of Mice with Sarcolysin Depending on Time of Appearance of Tumor after Transplantation

Time of appearance of tumor and injection of sarcolysin, days	Duration of survival of mice, days ($M \pm m$)		Significance of difference (P) in survival period of treated and untreated mice	Mean volume of tumor, %
	untreated	treated with sarcolysin		
7-8th	$52 \pm 2,7$ (15)	$63 \pm 3,0$ (11)	0,01	53
10-15th	$60 \pm 3,0$ (12)	$83 \pm 4,5$ (15)	$< 0,002$	43
17-20th	$75 \pm 2,9$ (15)	$68 \pm 3,5$ (15)	$< 0,01$	33
22-26th	$64 \pm 5,0$ (16)	$68 \pm 5,4$ (12)	0,05	68

Legend. Number of mice shown in parentheses.

EXPERIMENTAL RESULTS

On the 7th day after transplantation tumors were palpated in 18 of the 130 animals used in the experiments. Later the tumors continued to appear regularly until the 26th day after transplantation. By the end of the period of observation tumors were still not detected in 19 mice.

Curves of growth of the tumors, each plotted from data obtained on 11-16 mice, are shown in Fig. 1. Clearly there was hardly any difference in the rates of growth of tumors which appeared at different times after transplantation. The rate of growth of the tumors was reduced after injection of sarcolysin into the animals. In the case of tumors appearing on the 7th-10th day after transplantation retardation of tumor growth

was found on the 12th day after injection of sarcolysin. In the case of tumors appearing on the 10th-15th, 17th-20th, or 22nd-26th days after transplantation and receiving sarcolysin at these times, retardation of tumor growth was observed 3 days after injection of the compound.

The survival rate of the mice and the mean volume of the tumors on the 15th day after injection of sarcolysin were used as the indices of effectiveness of treatment of the mice with sarcolysin. Data for the volume of the tumors are given in Table 1 as ratios, in per cent, of the mean volume of the tumors in the treated mice and their mean volume in the untreated animals.

In the case of tumors appearing on the 7th-8th or 10th-15th day after transplantation and injection of sarcolysin a reduction in the mean volume of the tumors was observed in the treated mice compared with the untreated animals. Inhibition of tumor growth in the animals of this group was accompanied by an increase in their survival. These changes were most marked when tumors appeared and sarcolysin was injected on the 10th-15th day after transplantation.

In the case of tumors appearing on the 17th-20th day after transplantation the mean volume of the tumors in the treated mice on the 15th day after injection of sarcolysin was 33% of the volume of the tumors in the control group. However, a reduction in the size of the tumors was not accompanied by an increase in the survival period of the mice.

In the case of tumors appearing on the 22nd-26th day after transplantation injection of sarcolysin at that time did not give so marked a decrease in the volume of the tumors. Injection of sarcolysin did not affect the survival rate of the mice.

In the writers' opinion these results are interesting in connection with assessment of the optimal times for beginning cytostatic therapy.

LITERATURE CITED

1. A. Sh. Talipov, "The role of reactions of the body in the antitumor action of sarcolysin," Candidate's Dissertation, Moscow (1973).
2. V. Collins, K. Loeffler, and H. Tivey, *Am. J. Roentgenol.*, 76, 988 (1956).
3. M. Hosokawa, F. Sando, E. Gotohla, et al., *Gann*, 62, 67 (1971).
4. S. Kusama, T. Spratt, W. Donegan, et al., *Cancer (Philadelphia)*, 30, 594 (1972).
5. C. C. Zubrod, *Cancer Res.*, 29, 2284 (1969).