THE EFFECT OF DOPAN* ON VARIOUS ANIMAL TUMORS

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The works of L. F. Larionov and G. N. Platonova [4] have shown that the new, antitumorigenic preparation, 4-methyl-5-di (2-chlorethyl)-aminouracil (dopan) causes the steady resolution of fusiform sarcoma-45 in 90% of the rats treated. The great influence of dopan on this strain of tumor suggested that its effect on other animal tumors be studied. For this purpose, as well as sarcoma-45 [2], we used ten different strains of transplanted tumors, namely: rat tumors – M-1 and Tarashchansky's polymorphocellular sarcomas [9,7] and cancer of the uterus (Geren's tumor); mouse tumors – Crocker's sarcoma, Ehrlich's tumor (ascitic variant transplanted subcutaneously) [8], adenocarcinoma of the mammary gland (RSM strain) [6], solid carcinoma of the mammary gland (MAP strain) [1], transplanted cancer of the liver (hepatoma XXII) [3], mouse leukosis LIO-1 [5] and rabbit, Brown-Pearce carcinoma [8]. The antitumorigenic effect of dopan was also examined on rat sarcomas induced by 9, 10-dimethyl-1, 2-benzanthracene. The experiments were done on 274 rats, 506 mice and 31 rabbits.

EXPERIMENTAL METHODS

We did not begin the dopan therapy immediately after transplantation of the tumors, but waited until the tumors had reached a definite size. The rat tumors weighed about 1 g and the mouse tumors 0.1 g, i.e., each tumor was about 1% of the animal's body weight when the treatment was begun. In the experiments with the LIO-1 strain of leukosis and with the Brown-Pearce tumor, we began to administer the preparation a few hours or a day after transplantation. Dopan was administered to the rats per os in a dose of 0.3 mg per 1 kg of body weight daily, to the mice, in a dose of 0.4 mg per 1 kg of body weight daily and to the rabbits, in a dose of 0.75 mg per 1 kg of body weight every 72 hours. The treatment lasted 15-20 days, depending on the individual growth of the various tumors.

The experimental results were estimated according to the percentage of growth inhibition, calculated from the average weight of the tumors in the control and experimental groups. The data obtained was proven statistically by the Fisher-Student method. The percent of inhibition was considered true if the index, p, calculated according to this method, equaled 0,950 or more.

The criterion of the preparation activity in the experiments with leukosis was the average duration of the mice's life. In the experiments with the intravenous implantation of the Brown-Pearce tumor, the degree to which the internal organs were affected by the tumorous nodes was determined.

EXPERIMENTAL RESULTS

Table 1 gives the average data obtained from several series of experiments. Table 1 shows that sarcoma

* Russian trade name.

45 and Tarashchansky's sarcoma, in that order, were the most sensitive to dopan. The growth of Tarashchansky's sarcoma was inhibited 93% by dopan, and, in some of the rats (about 18%), dopan caused the resolution of the tumor.

Dopan inhibited the growth of the other experimental tumors, but did not cause their resolution. Table 1 gives the tumor strains in the order of their growth inhibition.

The study of dopan's effect on mouse leukosis, which was done on 150 mice, showed that this preparation had a weak antitumorigenic effect and prolonged the life of the mice in the experimental group by 20% as compared with the control.

When the Brown-Pearce tumor was implanted intravenously in the control rabbits, numerous tumors developed in the lungs, liver, kidneys and other internal organs, which led to the death of the animals on the 20th day after implantation. In two experiments on 31 rabbits, it was established that dopan considerably inhibited the development of the Brown-Pearce tumor in the internal organs (Table 2).

Table 2 shows that there were more tumor nodes in the internal organs of the control rabbits than in those of the experimental animals.

Therefore, the studies conducted indicate that dopan has a wide range of antitumorigenic action, affecting 12 different animal tumors. However, its degree of effectiveness varies. The antitumorigenic action of dopan was strongest on the two rat sarcomas – the fusiform sarcoma-45 and the polymorphocellular Tarashchansky's tumor – and on one rat carcinoma (Geren's tumor). Dopan moderately inhibited the development of the

TABLE 1

Effect of Dopan on Various Animal Tumors

Name of strain	Number of animals	Percent of inhibition	Proof of difference (criterion: p)
Sarcoma-45	80	100	1,0
Tarashchansky's sarcoma	40	93	1,0
Carcinoma of the uterus (Geren's tumor)	70	87	0, 978
Carcinoma of the mammary gland (MAP)	80	73	1,0
Ehrlich's tumor	117	69	0,99
M-1 sarcoma	70	64	1,0
Adenocarcinoma of the mammary gland (RSM)	80	57	1,0
Crocker's sarcoma	45	53	1,0
Induced rat sarcomas	14	51	0,877
Transplanted cancer of the liver (hepatoma XXII)	35	37	0,954

Brown-Pearce tumor and also moderately affected the growth of the polymorphocellular sarcoma M-1, the diffuse Ehrlich's tumor, Crocker's sarcoma, MAP carcinoma of the mammary gland and RSM adenocarcinoma of the mammary gland. A weak therapeutic effect was observed on cancer of the liver, mouse leukosis and on the induced rat sarcomas. Our experimental data does not permit the conclusion that the different degrees of sensitivity to dopan of the various tumors is explained by the difference in the histological structure of the tumors, since both epithelial and connective tissue tumors were found among the highly, moderately, and weakly sensitive strains. One must not exclude the possibility that still unstudied biochemical properties of the different tumor strains may have some bearing on the difference in the sensitivity of the various tumors to dopan.

TABLE 2

Effect of Dopan on Brown-Pearce Tumor

Control					Experiment				
No. of rabbits	Lungs	Liver	Kidneys	Other organs	No. of rabbits	Lungs	Liver	Kidneys	Other organs
Experiment I									
185	++++	++++	+	0	188	+	++	+	0
135	++++	+++	0	0	77	++	+	0	0
186	++	++	0	0	73	0	0	0	0
137	++	++	0	0	78	0	0	0	0
198	++++	0	0	0	136	0	0	0	0
					147	0	0	0	0
Experiment 2.									
31	++++	++	++++	+	61	+++++	+++	++	0
80	+++	+	+++	++	53	+++	+++	+++	0
41	++++	++++	+++	+	77	+++	+++	++	0
16	++++	++++	++	+	71	+	++	+++++	+++++
83	++++	++++	+++	0	92	+	+++	++	0
44	++++	++++	++++	0	78	+++	0	0	+
70	++++	+++	++++	+++	15	+	0	++	+
54	++	0	++	+	131	+	+	0	+
79	+++	0	0	0	95	+	+	0	0
20	++	0	0	0	22	0	0	0	+

Note: Intensity of tumorous affection in internal organs is designated as follows: + single tumor nodes (2-3); ++ a few tumor nodes (up to 10); +++ tumor nodes occupying 2/3 of the organ; ++++ tumor nodes throughout the entire organ.

SUMMARY

Dopan is effective in the treatment of twelve various experimental tumors. It is most effective in the treatment of fusiform sarcoma-45, Torashchansky's polymorphocellular sarcoma and carcinoma of the uterus in mice. The effect is moderate in case of Brown-Pearce tumors, polymorpho-cellular sarcoma M-1, Ehrlich's adenocarcinoma, Crocker's sarcoma and carcinoma of the mammary glands in mice. Little effect was observed in treating induced sarcoma in rats, leukosis of mice and cancer of the liver.

LITERATURE CITED

[1] Buvailo S. A., Pogosyants, E. E. and Shabad, L. M., Byull. Eksptl. Biol. i Med., 1946, Vol. 22, No. 1, pp. 8-10.

[2] Grushina A. A. and Laskina, A. V., Voprosy Onkol., 1954, No. 7, No. 7, pp. 157-167, Moscow, 1954.

[3] Gelshtein V. I., Voprosy Onkol., 1954, No. 7, pp. 172-180.

[4] Larionov L. F. and Platonova, G. N., Voprosy Onkol., 1955, No. 5, pp. 36-38.

[5] Malyugina L. L., Voprosy Onkol., 1954, No. 7, pp. 181-187.

[6] Pogosyants E. E., Byull. Eksptl. Biol. i Med., 1955, Vol. 39, No. 2, pp. 43-46.

[7] Tarashchanskaya F. Z., Med. Zhur. Ukraine, 1951, No.3, pp. 76-84.

[8] Fomenko M. M. and Ledanov, S. N., in the book: General and Specific Oncology, edited by Melnikova (in Russian), pp. 204-211, Moscow, 1940.

[9] Shabad L. M. and Blokh, M. I., Byull. Eksptl. Biol. i Med., 1947, Vol. 24, No. 4, pp. 246-249.