IRRADIATION OF ASCITES TUMORS OF THE OVARIES IN RATS UNDER HYPOTHERMIA

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Irradiation of the abdomen in rats with an ascites tumor of the ovaries inhibited growth of the tumor equally in the presence or absence of hypothermia. However, hypothermia weakened the effect of irradiation on the survival period of the animals.

An increase in the efficacy of radiotherapy of malignant neoplasms is largely dependent on the discovery of substances which can increase the "therapeutic interval," i. e., the difference between the radiosensitivity of tumors and normal tissues.

This paper examines the problem of the effect of hypothermia on the radiosensitivity of a transplanted tumor and of normal rat tissues.

EXPERIMENTAL METHOD

Albino rats of both sexes weighing 100-120 g, in which an ascites tumor of the ovaries was transplanted intraperitoneally (in a dose of 20 million cells), served as the test object. The effect of irradiation during hypothermia on subsequent growth of the tumor was studied in 48 rats. The animals were divided into four groups: 1) with no additional treatment; 2) hypothermia (14°) for 4 days after transplantation, followed by rewarming; 3) irradiation of the abdomen (1000 R) 4 days after transplantation; 4) irradiation plus hypothermia 4 days after transplantation. The total volume of ascites fluid and the concentration of tumor cells in it (with a Goryaev's chamber) were determined in animals of all the groups 7 days after transplantation of the tumor. By multiplying these figures, the total number of tumor cells was calculated.

The duration of survival after irradiation of the abdomen against the background of hypothermia was studied in 60 rats. These animals were divided into six groups: groups 1 and 2 were similar to those in series I, the rats of groups 3 and 5 were irradiated 4 days after transplantation of the tumor in doses of 850 and 700 R, respectively, under normal conditions; while the rats of groups 4 and 6 were similarly irradiated against the background of hypothermia.

Hypothermia was produced by Gye's method. The closed box, with a capacity of 2 liters, containing the rat was placed in a refrigerator at 5° until the rectal temperature fell to about 18° under the conditions of progressive hypercapnia and hypoxia. The animal was then taken from the box, and by applying ice to the trunk, its temperature was lowered further to 14°. Artificial rewarming was combined initially with rhythmic compression of the chest to stimulate cardiac activity and respiration.

Contitions of irradiation: RUM-17 apparatus, voltage 180 kV, current 15 mA, filter 3 mm Al, half-attenuation layer 0.3 mm Cu, distance from source to skin 20 cm, dose rate 600 R/min.

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TABLE 1. Indices of Growth of Ovarian Tumor in Rats Treated in Different Ways (M ± m)

Character of treatment	Volume of ascites fluid, ml	Concentration of tumor cells (10^6/ml)	Total No. of cells (in millions)
No treatment	30,6±3,8	67,3±5,9	1907±178
Hypothermia (14°)	30,9±3,0	60,6±4,1	1818±164
Irradiation (1000 R)	10,2±1,1	105,6±8,8	1031±117
Irradiation (1000 R) with hypothermia (14°)	12,9±1,1	79,2±8,5	945±79

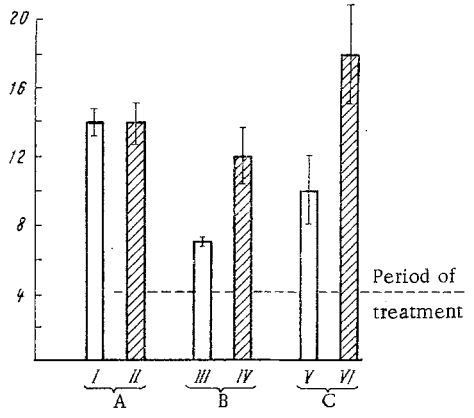

Fig. 1. Mean survival period (in days) after transplantation of tumor into rats of different groups. Shaded columns represent animals subjected to hypothermia; A) without irradiation; B) 850 R; C) 700 R.

EXPERIMENTAL RESULTS

The indices of tumor growth in the animals of group 2 were identical with those in group 1 (Table 1). In other words, these results agree with those in the literature (2, 7, 10-12) indicating that hypothermia itself has no effect on the course of growth of a tumor. As would be expected, irradiation sharply reduced the volume of ascites fluid and the total number of tumor cells ($P < 0.001$), while hypothermia caused practically no change in the severity of radiation damage to the tumor. This is in good agreement with previous findings when rats with a primary solid RS-1 tumor were irradiated under hypothermia [1, 8, 9].

Somewhat different results were obtained by the study of the survival period of the different groups of animals. Rats receiving a single exposure to hypothermia died from progressive growth of the tumor at the same time as animals receiving no treatment (Fig. 1). Irradiation of the tumor (in doses of 700 R and, in particular, 850 R) merely shortened the period of survival; the cause of death was the development of radiation sickness of the gastro-intestinal syndrome type. However, hypothermia considerably weakened the effect of irradiation on the survival period of the experimental animals. In group 4, for instance, compared with group 3 (850 R), the survival period on the average was 5 days longer ($P < 0.01$), while in group 6 it was 8 days longer than in group 5 (700 R; $P < 0.05$). The animals of group 6 on the average survived for 4 days longer than untreated animals. Hypothermia thus gave a definite radioprotective effect on the normal tissues. This conclusion is in good agreement with published data [3, 4, 6, 13].

The radiomodifiers which have been studied most closely are the oxygen tension in the tissues and the tissue concentration of sulfhydryl groups. The writers' investigations [5, 9] have shown that in rats cooled by Gye's method to 14°, the pO_2 falls and the concentration of sulfhydryl groups is reduced both in normal tissues and in the tumor. It is not yet clear why the radiosensitivity of the tumor is not reduced under these circumstances.

LITERATURE CITED

1. V. A. Bernshtein and M. T. Chulanova-Nurkina, Trudy Kazakh. Inst. Onkol. i Radiol. (Alma-Ata), No. 4, 109 (1967).
2. F. A. Gluzman, in: Problems of Hypothermia in Pathology [in Russian], Kiev (1959), p. 191.
3. N. V. Gordeicheva and T. P. Strokova, Radiobiologiya, No. 5, 747 (1968).
4. G. N. Il'yutkin and L. P. Dymnikova, Med. Radiol., No. 9, 46 (1964).
5. S. K. Kauashev, M. T. Chulanova-Nurkina, Kh. A. Akhmetbekova, et al., Trudy Kazakh. Inst. Onkol. i Radiol. (Alma-Ata), 6, 219 (1969).
6. M. M. Konstantinova, Dokl. Akad. Nauk SSSR, 138, 223 (1961).
7. S. P. Sizenko and V. V. Markevich, Vrach. Delo, No. 1, 53 (1958).
8. M. T. Chulanova-Nurkina, Trudy Kazakh. Inst. Onkol. i Radiol. (Alma-Ata), 6, 215 (1969).
9. M. T. Chulanova-Nurkina, Irradiation of a Primary Tumor under Hypothermic Conditions, Candidate's Dissertation, Alma-Ata (1970).

10. J. Ariel and S. L. Warren, Cancer Res., 3, 464 (1943).
11. F. Bischoff, M. L. Long, and J. J. Rupp, Am. J. Cancer, 39, 241 (1940).
12. S. Grollman and M. F. Crass, J. Appl. Physiol., 21, 1201 (1966).
13. S. Hornsey, Proc. Roy. Soc. B, 147, 547 (1957).