COMBINED ACTION OF SHF HYPERTHERMIA AND X RAYS ON GROWTH OF SARCOMA 45

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UDC 616-006.3-04-085.849.122+615.849.114]-036.8

Good results have recently been obtained by the use of hyperthermia in clinical and experimental oncology, both separately and in conjunction with ionizing radiation and chemotherapy [1, 3, 4, 7]. However, the optimal conditions for the use of these factors (dose, fractionation) have not yet been adequately studied and data on dependence of the antitumor effect on the order of application of hyperthermia and ionizing radiation are contradictory [5, 10].

In the investigation described below the effect of combined exposure to superhigh-frequency (SHF) hyperthermia and **x rays** on sarcoma 45 was investigated in relation to the stage of tumor growth and the effectiveness of total and local hyperthermia was compared.

EXPERIMENTAL METHOD

Noninbred male rats weighing 180-200 g were inoculated subcutaneously in the right thigh with a solid tumor (sarcoma 45) [2]. Depending on the experimental conditions, the rats with tumors were irradiated on the 10th-45th days after inoculation of the tumor. The source of SHF radiation **was a Luch-58 physiotherapy** apparatus (2375 MHz). Irradiation was carried out in the reactive zone. Temperature was recorded by means of the KSP-4 potentiometer (the temperature probe was an MT-54 thermistor, fitted into an injection needle), the probe being inserted into the center of the tumor in the direction of spread of the SHF field, while the SHF generator was temporarily switched off. During local SHF irradiation the animal's body was screened **with Luch-50 radiation** absorbing material, and only the limb with the tumor was located in the field of irradiation. The duration of microwave irradiation was 30 min and the temperature in the tumor 41.5-42.5°C. During whole-body SHF irradiation (30 min, 40-41°C) the rectal temperature was recorded. The source of ionizing radiation was the RUM-17 x-ray therapeutic apparatus (current 15 mA, voltage 200 kV, filter 0.5 mm + 1 mm Al, dose rate 0.87 Gy/min. The single dose of x rays was 8 Gy. The interval between SHF hyperthermia and x-ray irradiation was 2-3 min. The efficacy of the combined **action of hyperthermia** and x-ray irradiation was estimated by the change in volume of the tumor [9] and the coefficient of inhibition of tumor growth.

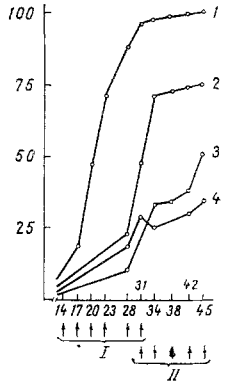

Fig. 1. Effectiveness of six applications of SHF hyperthermia and **x rays** to sarcoma 45 depending on stage of tumor growth. Abscissa, time after inoculation of tumor (in days); ordinate, coefficient of inhibition of tumor growth. Arrows indicate time of irradiation in the early (I) and late (II) stages of growth. 1, 3) Combined exposure to SHF hyperthermia and **x rays**; 2, 4) exposure to x rays only. Irradiation began on 14th (1, 2) and 28th (3, 4) days of tumor growth.

KEY WORDS: superhigh-frequency hyperthermia; **x rays**; sarcoma 45.

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(Presented by Academician of the Academy of Medical Sciences of the USSR P. D. Gorizontov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 91, No. 4, pp. 471-473, April, 1981. Original article submitted October 8, 1980.

0007-4888/81/9104-0511$07.50

TABLE 1. Changes in Volume and Weight of Sarcoma 45 3 Days after Triple Exposure (on 10th, 12th, and 14th days after inoculation) to Combined and Separate Local SHF Hyperthermia and X-Ray Irradiation (M ± m)

Group of animals	Treatment applied	Volume of tumor, cm^3	Weight of tumor, g
1	X-ray irradiation + SHF hyperthermia	0,59±0,15† (74)	0,71±0,05† (68)
2	SHF hyperthermia + x-ray irradiation	0,63±0,14† (72)	0,80±0,24† (64)
3	X-ray irradiation	0,81±0,10* (64)	0,87±0,15† (61)
4	SHF hyperthermia	1,44±0,21 (36)	1,93±0,28 (14)
5	Control (no treatment)	2,25±0,54	2,26±0,48

*Difference significant ($P < 0.05$) compared with group 5.
†Difference significant compared with groups 4 and 5.
Legend. Here and in Table 2, coefficient of inhibition of tumor growth (in %) given in parentheses.

TABLE 2. Changes in Volume (in cm^3) of Sarcoma 45 after Single Combined Exposure (on 23rd day after inoculation) to Whole-Body or Local SHF Hyperthermia and X-Ray Irradiation (M ± m)

Group of animals	Treatment applied	Time after inoculation of tumor, days		
		23	40	53
1	Total SHF hyperthermia + x-ray irradiation	0,56±0,19	2,29±0,98* (56)	4,31±1,81 (58)
2	Local SHF hyperthermia + x-ray irradiation	0,69±0,28	0,77±0,39* (85)	0,89±0,38* (91)
3	Control (no treatment)	0,58±0,09	5,30±1,29	10,42±4,10

*Difference significant ($P < 0.05$) compared with group 3.

EXPERIMENTAL RESULTS

Microwaves irradiation raised the temperature in the tumor in the course of 3-5 min to 42.5°C and kept it at 41.5-42.5°C for as long as required. There was no change in the rectal temperature under these circumstances.

As Table 1 shows, the order of treatment with SHF hyperthermia and x-ray irradiation did not significantly influence the efficacy of combined treatment. This is in agreement with data [5] showing that the synergism of combined exposure to heat and radiation persists for several hours regardless of the order of their application, but it contradicts information [10] suggesting that heat treatment is more effective during the period from 30 min to 6 h after application of ionizing radiation.

There is experimental evidence [5] that smaller tumors are more radiosensitive and larger tumors are more temperature-sensitive. The comparative study of the effects of exposure to SHF hyperthermia and x rays at different stages of growth of sarcoma 45 showed that sensitivity of the tumor to combined hyperthermia and x-ray therapy is highest in the early stage of growth (Fig. 1). The leading factor is the radiosensitivity of the tumor, for by contrast with the existing data [5], the sensitivity of sarcoma 45 to SHF hyperthermia in the late stage of growth did not differ significantly from that in the early stage. Combined exposure to six sessions of SHF hyperthermia and x-ray irradiation in the early (logarithmic) stage of growth of the tumor was sufficient to ensure its complete absorption.

In clinical practice whole-body hyperthermia, with the exception of the head, by means of various physical factors is used for the treatment of malignant neoplasms [1, 7]. Meanwhile, the problem of the effect of hyperthermia of organs and systems not directly related to the tumor on the effectiveness of antitumor measures is still undecided. Accordingly the effectiveness of whole-body SHF hyperthermia (rectal temperature 40-41°C) and local SHF hyperthermia (41.5-42.5°C in the tumor), combined with local x-ray irradiation, was compared. The results (Table 2) showed that a combination of whole-body SHF hyperthermia with local x-ray irradiation can achieve significant inhibition of tumor growth, although the effect in this case was much less than after local SHF hyperthermia. The high efficacy of local SHF hyperthermia is evidently due to the fact that under these circumstances the optimal radiosensitizing temperature (42°C [7]) is obtained, whereas during whole-body hyperthermia the body temperature cannot be raised above 40-41°C without the risk of death of the irradiated animal.

The results obtained with experimental sarcoma 45 thus indicate that repeated fractional combined local SHF hyperthermia with x-ray irradiation, irrespective of the order in which the factors are applied, can result in the practically complete absorption of the tumor in the logarithmic stage of its growth.

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ORIGIN OF IMMUNOGLOBULINS BOUND WITH SURFACE MEMBRANES OF MALIGNANT CELLS IN SOME NONLYMPHOID FORMS OF ACUTE LEUKEMIA IN MAN

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UDC 616.155.392-036.11-07:616.155.3-097.5-078.7

In malignant neoplasms of varied tissue origin, in both man and animals, the tumor cells acquire the ability to bind on their surface antibodies against various classes of immunoglobulins (Ig), mainly IgG [5, 9, 11, 14]. Malignant cells of tumors of hematopoietic tissue — acute human myelo-, myelomono-, and monoblastic leukemias (OML, OMML, and OMoL respectively) possess the same property [1, 2, 6]. No Ig have been found on membranes of immature cells of the normal myelomonocytic series of hematopoiesis [10], and for that reason the fact that anti-Ig-antibodies are bound by blast cells in these forms of acute leukemia is difficult to explain and is of considerable interest.

The object of the present investigation was to study structure-binding antibodies against different classes of Ig on the surface membranes of Ig-positive [2] blast cells in certain forms of acute leukemia in man.

EXPERIMENTAL METHOD

Peripheral blood leukocytes from four patients with OMML and two patients with OMoL, taken in the acute period of the disease before the beginning of cytostatic chemotherapy, and preserved in a viable state at −196°C were studied. The leukocyte preparations contained 53-95% of blast cells.

Ability of the membrane to bind anti-Ig-antibodies was estimated by the direct immunofluorescence test (DIT) [2], using goat antisera against human IgG, IgM, IgA, and IgD, labeled with fluorescein isothiocyanate (**Behringwerke, West Germany**).

The presence of receptors for the Fc-fragment of IgG (FcR) on the surface of the cells was determined by rosette-formation with sheep's red blood cells sensitized with rabbit antierythrocytic antibodies [7].

KEY WORDS: leukemia; immunoglobulins.

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(Presented by Academician of the Academy of Medical Sciences of the USSR N. A. Fedorov.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 91, No. 4, pp. 473-476, April, 1981. Original article submitted March 13, 1980.