

EFFECT OF ADRENALIN AND CYCLOPHOSPHAMIDE ON GROWTH AND
BLOOD SUPPLY OF EXPERIMENTAL GUÉRIN'S CARCINOMA

L. I. Khananaev and S. A. Fitsych

UDC 616-006-085+615.771.7

In experiments on albino rats inoculated with experimental Guérin's carcinoma, methods of injecting the blood vessels followed by the preparation of sections, unstained and stained with hematoxylin and eosin, were used to determine the density of the capillary network and the coefficient of inhibition of growth of the tumor. They showed that intramuscular injections of adrenalin inhibit growth of Guérin's carcinoma and, at the same time, increase the intensity of its microvascularization. The combined administration of cyclophosphamide and adrenalin gave a marked antitumor effect as the result of potentiation of the antitumor action of cyclophosphamide by adrenalin. The direct relationship shown between the intensity of the blood supply to the Guérin's carcinoma, the density of arrangement of the capillaries, and the therapeutic effect of cyclophosphamide and adrenalin points to the role of the blood stream in the antitumor action of cyclophosphamide when administered together with adrenalin.

Key words: Guérin's carcinoma; blood supply; inhibition of tumor growth; cyclophosphamide; adrenalin.

The microvascularization of individual tumors has been the subject of several investigations [3, 4]. Potentiation of the antitumor action of thiophosphamide and dipin on sarcoma 45 by adrenalin has been found [5, 6].

In the investigation described below the effect of adrenalin and cyclophosphamide on growth and the blood supply of primary Guérin's carcinoma was studied.

EXPERIMENTAL METHOD AND RESULTS

Experiments were carried out on 75 albino rats. During growth of the carcinoma and administration of adrenalin (0.15-0.2 ml of a 0.1% solution in ampules injected intramuscularly as one or three injections daily, starting from the 10th day after transplantation), of cyclophosphamide (intramuscularly 4-5 mg/100 g body weight, once every 4 days starting on the 15th day after transplantation), and a combination of adrenalin and cyclophosphamide (both given at the same time, starting from the 15th day after transplantation, once every 4 days for 15 days) the mean diameter of the tumor [7], the coefficient of antitumor activity [2], and the density of the capillary network [1] were measured. On the 5th-30th day the blood vessels of the tumor were injected with a suspension of Paris green in chloroform and ether and cleared sections and sections stained with hematoxylin and eosin were obtained from different parts.

During growth the Guérin's carcinoma develops its own vascular system which is distributed among the various zones. Since capillary formation lags behind the processes of proliferation of the tumor cells, parts of the central and intermediate zones by the 15th and 20th days of growth of the tumor were without sources of blood supply, and this was accompanied by death of the capillary networks, deformation of the blood vessels, necrobiosis, and necrosis. During treatment with cyclophosphamide the Guérin's carcinoma quickly decreased in size, arterio-venous anastomoses were opened, blood vessels were dilated, and the density of the capillary network of the tumor was increased. On the 20th day after transplantation, after 18 injections of adrenalin, abundant vascularization was observed in the peripheral zone and capsule of the

Department of Histology and Embryology, Ivano-Frankovsk Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Kupriyanov.) Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 79, No. 3, pp. 83-84, March, 1975. Original article submitted May 16, 1974.

© 1975 Plenum Publishing Corporation, 227 West 17th Street, New York, N.Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for \$15.00.

tumor, where many newly formed capillaries could be seen and where previously invisible anastomoses were revealed. Postcapillaries, surrounding the necrobiotic areas, gradually joined together to form venules and veins. On the 25th-30th day of the experiments (25-30 injections of adrenalin) the number of vessels in the peripheral zone of the tumor increased considerably. No vessels were seen in the central zone of the tumor. Adrenalin, in the above-mentioned dosage, had a marked antitumor action (by the 30th day the coefficient of activity was +61%; $P < 0.001$). After combined administration of adrenalin and cyclophosphamide, the retardation of growth of the Guérin's carcinoma was much greater than after the separate administration of these substances (coefficient of activity of cyclophosphamide +82%; $P < 0.001$; coefficient of activity for combined administration of adrenalin and cyclophosphamide +85%; $P < 0.05$). Under these conditions the lumen of the venous blood vessels of the tumor was greatly dilated, the density of the capillary networks was increased, and the arterio-venous anastomoses of the Guérin's carcinoma and the tissues surrounding it were opened.

These experiments thus showed that adrenalin has an inhibitory action on a growing Guérin's carcinoma, accompanied by an increase in the degree of microvascularization of the tumor connected with the decrease in its size. Combined administration of cyclophosphamide and adrenalin gave a marked antitumor effect as the result of potentiation of the antitumor action of cyclophosphamide by adrenalin. The direct relationship discovered between the intensity of vascularization of the Guérin's carcinoma, the density of the capillary network, and the therapeutic effect of cyclophosphamide and adrenalin points to a role of the vascular system in the antitumor action of these substances.

LITERATURE CITED

1. S. M. Blinkov and G. D. Moiseev, Dokl. Akad. Nauk SSSR, 140, No. 2, 465 (1961).
2. A. A. Grushinina, in: Methods of Experimental Therapy [in Russian], Moscow (1959), p. 390.
3. D. A. Zhdanov and N. V. Krylova, in: Problems in the Collateral Circulation from the Functional and Anatomical Aspects [in Russian], Ivano-Frankovsk (1964), p. 371.
4. N. V. Krylova, Arkh. Anat., No. 1, 76 (1966).
5. V. A. Chernov and S. M. Minakova, Vopr. Onkol., No. 1, 62 (1971).
6. Zh. F. Presnova and V. A. Chernova, Byull. Éksperim. Biol. i Med., No. 10, 90 (1964).
7. B. Schreck, Am. J. Cancer, 24, 807 (1935).