Anticarcinogenic Effect of Palustran on Rat Tumors Induced by 3-(1-α-L-Arabinopyranosyl)-1-Methyl-1-Nitrosourea (AMNU)

N. I. Sherenesheva, V. E. FinTko, F. F. Blanko, T. A. Alieva, E. N. Bedrina, I. A. Gogoleva, and T. I. Klochkova

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The study explores the effect of palustran on AMNU-induced carcinogenesis in rats. Palustran significantly reduced the total incidence of neoplasms and the incidence of kidney tumors. These data suggest that palustran can be beneficial in preventing new primary tumors in tumor patients treated with nitrosalkylurea analogs.

Key Words: *palustran; tumor; kidney*

Physiological functions and the role of dietary fibers, such as vegetable nonstarch polysaccharides and lignin, in human pathology [2-4], in particular, malignant neoplasms [1] are well established. Data of epidemiological, experimental, and clinical studies suggest that increased consumption of dietary fibers and the use of fiber-containing additives and drugs reduces the risk of tumor of the large intestine and, probably, of some other tumors, in particular, breast cancer [1].

The aim of the present study was to investigate the effect of long-term treatment with palustran, a heteropolysaccharide of high-molecular-weight fraction from *Comarum palustre* (Rosaceae family), on carcinogenic action of AMNU. Our preclinical *in vivo* studies on 12 transplanted tumor strains demonstrated considerable antitumor activity of palustran against Ca-755 and AKATOL adenocarcinomas, B-16 melanoma, S-180 sarcoma; W-256 carcinoma, and S-45 sarcoma. Palustran potentiates carcinogenic activity of cytostatics without increasing their toxic effects. Due to its broad and dose-independent antitumor activity, the possibility of combined administration with cytostatics, the absence of toxic effects, and the ability of inducing endogenous interferon production and stimulating cytolytic activity of T cells, palustran can be considered as a modulator of antitumor immunity and potential prophylactic antitumor drug.

MATERIALS AND METHODS

The antitumor preparation AMNU synthesized at the Oncology Research Center was used in experiments. Palustran was extracted from vegetable material with 86% ethanol, purified on a KU-2 ion-exchange resin, and precipitated in various solvents. Experiment was performed on 80 random-bred female albino rats (initial weight 130-180 g). The rats were maintained in plastic cages (5 rats per cage) and fed standard diet. Groups 1 (n=20) and 4 (n=15) received 100 mg/kg palustran and group 2 (n=20) received 50 mg/kg palustran 3 times per week (with chow). Groups 1, 2, and 3 (n=15) received single intravenous injection of 250 mg/kg AMNU. Group 5 rats (n=10) served as intact controls. The animals were monthly weighted. Palustran treatment was started 1 month before AMNU injection and was continued for 10 months, after that all animals were sacrificed and subjected to pathological examination. Fragments of tumors were fixed in neutral formalin and embedded

Institute of Experimental Diagnostics and Therapy of Neoplasms, N. N. Blokhin Oncology Research Center, Russian Academy of Medical Sciences, Moscow

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TABLE 1. Effect of Palustran on AMNU-Induced Carcinogenesis in Rats (*M±m*)

Number of animals	Group		
	group 1: AMNU+palustran (100 mg/kg)	group 2: AMNU+palustran (50 mg/kg)	group 3: AMNU
With tumors[1]	3* (15)	4 (20)	6 (40)
With multiple tumors[2]	—	2 (50)	2 (33.3)
With mesenchymal renal tumor	—	1* (5)	4 (26.6)
With breast fibroadenoma	1	3	1
With skin sarcoma	1	1	2
With mesenterial sarcoma	1	—	—
With duodenal sarcoma	—	1	—
Latency, days	206±18	232±0	200±23

Note. [1]With respect to total number of rats before the first tumor was detected; [2]with respect to the total number of tumor-bearing rats. Percentage is shown in parentheses. *$p<0.05$ compared with group 3 (χ^2 test).

in paraffin. Sections were stained with hematoxylin and eosin. The data were processed statistically using Student-Fisher and χ^2 tests with Yates correction for small samples [6].

RESULTS

Single intravenous injection of AMNU in a dose of 250 mg/kg induced tumors in 6 out of 15 rats (Table 1). Total occurrence of neoplasms in this group was 40%. Tumors were found mainly in the kidneys (in 4 of 15 rats, 26.6%) and less frequently in other organs. Renal tumors were predominantly bilateral and varied from small to huge tumors occupying the major part of the abdominal cavity. Histologically, these were mesenchymal tumors with various tissue-specific differentiation signs. Palustran reduced the total occurrence of neoplasms and the incidence of AMNU-induced tumors. For instance, in group 2 rats treated with 50 mg/kg palustran the total occurrence of neoplasms decreased from 40 to 20%, while the incidence of renal tumors decreased from 26.6 to 5% ($p<0.05$). In animals receiving 100 mg/kg palustran the total occurrence of neoplasms decreased to 15% ($p<0.05$) and no renal tumors were found ($p<0.05$). There were no multiple tumors in this group. Latencies of tumor development were similar in all these groups.

However, it should be noted that first tumors in groups 1 and 2 were found on days 191 and 232, respectively, i.e., 23 and 64 days later that in group 3. Palustran had practically no effect on morphological features of AMNU-induced tumors: they retained histological structure characteristic of tumors induced by these nitrosourea derivatives [5,7]. Rats receiving only palustran and intact rats had no tumors.

Thus, our experiments demonstrated that palustran reduced carcinogenic effect of AMNU. AMNU, a member of the nitrosoalkylurea family, is recommended for the treatment of skin melanoma (Protocol of Pharmacological Committee of the USSR, No. 3, February 14, 1990). Clinical use of nitrosoalkylurea derivatives pose the problems of preventing their toxicity and delayed biological effects.

It has been shown that even single AMNU injection induces tumor growth in experimental animals [7]. Anticarcinogenic effect of palustran observed in our experiments suggests that this preparation can be used for reducing the risk of new primary tumors in patients treated with nitrosoalkylurea analogs and for preventing primary tumors in persons contacting with AMNU due to their professional activity.

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