PROGNOSTICATING AND PHARMACOLOGICAL PROPHYLAXIS OF RADIOGENIC MALIGNANT TUMOURS

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Cancerogenic effect risks due to ionizing radiation, that impacted on large population groups because of Chernobyl and other accidents, cause the actuality of early diagnosis problems and of radiogenic tumour prevention. Since cancero-embryonic antigen and α-fetoprotein had been found, the tumour markers began to be frequently used by oncologists. However, attempt to use onco-markers, as test for earlier pre-clinic determination, have been unsuccessful. The secondary messengers of hormonal signal, cyclic nucleotides, that take the leading place in system of organism self-regulation, had attracted our attention. As known, the increase of cell division number and suppression of morphological and biochemical developments of differentiation are the fundamental characteristics of tumour growth and are proceeding together with participating of cyclic nucleotide system. The including of both nucleotides in neoplastic transformation and at the same time their constant presence in extracellular fluid (blood serum, urine) makes the perspective use of these compounds as indicators of tumour growth before the appearance of clinic signs of diseases. This coincides with the modern viewpoints on the developments of optimum programs for pre-clinic diagnosing of tumours, that needs to base on the change in homeostasis preceded the malignant tumour development (1).

The check of ability of nucleotide ratio test to give the information for prognosis of onco-diseases has been conducted in experiments on the *Wistar* rats, and allow to observe the cancerogenesis process from tumour growth induction through its outcomes during a cohort lifetime that was maximum short period - 650-700 days. Animals were exposed to γ-radiation at accumulated doses of 10 and 20 Gy, under which the malignant tumour frequency increased up to 65% (in control group up to 25%). The contents of cyclic AMP and cyclic GMP in urine were determined in each rat in 10 months after exposure (time of tumour outcome) and further in each 2 month up to natural death by using *Amersham* Kits. The postmortem diagnoses were determined by histologic methods. Results of retrospective analysis evidence that the increasing of cAMP/cGMP ratio was being observed in urine of animals, that had tumours, long before their deaths and independently from tumour localization. This period may be formally recognized as pre-clinic, and it includes different stages of tumour growth. The increase of the ratio was being due to both the reinforcement of cAMP excretion and decreasing of cGMP excretion. The data base on rats, that had the tumour, was processed statistically for obtaining the objective evaluation of possibility to use this test for pre-clinic tumour growth diagnoses. It was shown that test has the high diagnostic sensitivity (85%) and the high ability of prognosticating positive result (73%) as well as the satisfactory diagnostic effectiveness (68%). In special experiment, we have applied the prospective approach to data analysis. We assumed that the positive tumour diagnosis is recognized *a priori* during lifetime on the base of the registered increasing of cAMP/cGMP ratio. Diagnoses have been verified after animal death by histologic methods. The results of comparison between the biochemical prognosis and histologic diagnosis indicated that the coincidence was in 87% of cases. We think that the increase of cAMP/cGMP ratio, observed in urine of rats with tumour, evidence

there is the "accident regulation" start, which is used for preservation of homeostasis on new level and for control of differentiation in spite of tumour growth (2).

Basing on our conducted studies, we took out the patent for the method to find out the tumoural process in experimental animals (3). The similarity of molecular and cellular mechanisms of malignant transformation in animals and persons, and the same tissue response following the genotoxic factor influence have allowed us to begin the clinic test of this method. For this purpose, the group of high risk of malignant disease development have been selected in "Mayak" PA personnel, the first atomic complex in our country. Part of the group had been exposed to radiation at doses exceeded the maximum permissible dose at early stages of production organization, and now these individuals are at age of realization of malignant tumours.

At the same time we are conducting the studies of prevention of induced tumour diseases. The effectiveness of the medicinal preparation to prevent or to decrease the frequency of spontaneous and chemical cancerogens-induced tumours have been shown in the experimental and epidemiological studies (4,5). However, the scientific developments of the radiation cancerogenesis prophylaxis are not numerous.

We are developing the methodology to conduct the pharmacological prophylaxis of radiation cancerogenesis basing on the experimental models of chronic influence of different kinds of ionizing radiation. These models if taking into consideration the dose characteristics, were approached to conditions of occupational exposures and radionuclide influence on the contamination territories following the radiaiton accidents. The developing methodology allows for peculiarities of radiation cancerogenesis under the influence of incorporated α- and β-emitters (transuranium nuclides, tritium). These include the forming of tumour process under conditions of increased burden for antioxidant system and the corresponding increase of organism necessity of antioxidant substances. Further, the cancerogenic metabolite contents are increased because of damage of monooxygenase system P-450 of liver following the organism exposure and especially the incorporation of transuranium nuclides. In addition, the radiogenic tumour development goes frequently on the background of damage of the general and/or local immunity. The insufficiency of this system, as known, is the strong promoter of oncogenesis. Basing on the traits of radiation cancerogenesis, the medicinal preparations are selected, and their application regimen is determined (time period, pattern, and duration) for purpose of prophylaxis of tumour growth.

The approbation of the developing methodology was conducted in experiments with *Wistar* heterozygous rats and *CBA* inbred mice. The prophylactic effectiveness of medicinal preparations with different mechanisms of action (antioxidants, immunomodulators) was studied under different ways of one-time intake of plutonium-239 and under long-time (during 1/3 of lifetime) injection of tritium oxide. The preliminary findings in experiment with 391 rats indicated that the ration enrichment by β-carotin (2 mg per day) or by its complex with α-tocopherol (1 mg per day) did not modify the spontaneous cancerogenesis during all period of observation. At the same time, the using of β-carotin in 750 animals exposed to α-radiation of incorporated plutonium-239 after inhalation intake (plutonium-239 citrate, the lung absorbed doses of 240- 404 cGy) decreased the general frequency of malignant tumours in rat males at 1.5 times (48%; in control group - 72.3%) due to mainly the decreasing of lung cancer frequency. The frequency modification of osteosarcomas induced by α-exposure of bone tissue to incorporated plutonium-239 was also found only in rat males that had β-carotin and α-tocopherol in ration during all lifetime after inhalation, decreases were for standard ration - up to 30%, and for ration with vitamins - up to

5%. The β-carotin and its complex with α-tocopherol did not influence on plutonium-239-induced oncogenesis of rat females. The dependence of this preparations' modification effect from sex has been shown in other papers (6).

The distinct onco-prophylactic effect of β-carotin was also revealed on the basis of experimental model of even β-exposure of 250 *CBA* mice to incorporated tritium. The receiving of this preparation with feed (1 mg per mouse 3 times per week) during all period of radionuclide influence (6.5 months, the absorbed dose of 8.7 Gy) decreased the induced malignant tumour frequency at 1.5 times in comparison with exposure control (38.3% and 58.6%, respectively). Most demonstrative decrease was for lung cancer - 1.6% and 13.3%, respectively.

The immunomodulating preparations modified the radiogenic tumour frequencies when they were used at period of radiation damages in immune system (1350 *CBA* mice, and 800 *Wistar* rats). Myelopid (MP), produced at the Immunology Institute, Moscow, was being received by *CBA* mice exposed to β-radiation (the absorbed dose of 8.7 Gy) weekly during 3.5 months (0.5 mo. - the end of HTO intake, and 3 mo. - period after the intake end) in summary amount 700 μg per mouse ; and decreased the frequency of induced myeloleukemias at 3.6 times (up to 4.4% vs 16% in exposed control), and of lung cancer at 1.7 times (7.3% and 13.3%, respectively). However, the decreasings of the MP intake up to one-time per month and summary amount up to 300 μg per mouse during 3 months led to the decrease of MP effectiveness. The dependence of onco-prophylactic effect of MP from the pattern of intake and from received preparation amount has been also shown for α-exposure to incorporated plutonium-239 intake into blood flow. The decreasing of induced tumour frequency in organs of main deposition of radionuclide (liver, skeleton) has been only in case of using the first scheme of the MP receiving.

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