

RECENT ADVANCES IN CHEMOTHERAPY

**Proceedings of the
18th International
Congress of Chemotherapy**

**Stockholm, Sweden
June 27 - July 2, 1993**

Editors:

Jerzy Einhorn
Department of Oncology, Karolinska Hospital
Karolinska Institute, Stockholm, Sweden

Carl Erik Nord
Department of Immunology, Microbiology, Pathology
and Infectious Diseases, Huddinge Hospital
Karolinska Institute, Stockholm, Sweden

S. Ragnar Norrby
Department of Infectious Diseases, University Hospital
University of Lund, Lund, Sweden

American Society for Microbiology
Washington, D.C.

Experience of the Application of Ukrain in Oncological Practice in Ukraine

V. S. ZEMSKOV, O. YA. YAREMCHUK, YA. M. SUSAK,* E. R. DENFKA, O. V. KRAVCHENCO, and L. YA. KAMENETS

Department of General Surgery, Department of Oncology, Ukrainian State Medical University, Kiev, Ukraine

Starting from 1992, the Departments of General Surgery and Oncology of Ukrainian State Medical University have been carrying out investigations on the application of the preparation Ukrain in oncological patients. Ukrain is a chelidone thiophosphoric acid derivative, Tris[2-[[5bS-(5ba,6b,12ba)]-5b,6,7,12b,13,14-hexahydro-13-methyl[1,3]benzodioxolo[5,6-c]-1,3-dioxolo[4,5-i]phe-nanthridinium-6-ol]ethanaminil]phosphinesulfide-6HCl. Its immunostimulating and antineoplastic properties *in vitro*, *in vivo*, and in clinical practice are widely reflected in the literature (2-4, 6). These properties of Ukrain are of particular importance for the Ukraine, which is still suffering the harmful influence of the consequences of the accident at the Chernobyl nuclear power station (prolonged influence of small doses of radiation, accumulation of radionuclides in an organism). These post-accident after-effects lead to damage in the immune T-system and especially in the system of natural killer cells responsible for anticancer and antiviral defense (1, 5, 7). The opportunity of carrying out this research was granted by the Ukrainian Anticancer Institute, Austria.

The aim of the research was the further study of the action of Ukrain upon oncology patients under conditions of harmful anthropogenic factors.

Patients. Twenty-three oncological patients were treated with Ukrain (12 males and 11 females). Average age was 52 years. A description of the cases (diagnoses and staging after the TNM classification) is given in Table 1.

Treatment. All the patients were administered Ukrain intravenously in a dose of 10 mg (two ampules with 5 mg of the preparation each) every second day to a total dose of 100 mg. An interval of 10 days followed the first course of treatment, and then the identical course was repeated. In 17 cases the first course of treatment was followed by an operation, and 10 days after that the second course of treatment was carried out. No chemotherapy or X-ray therapy was conducted in any of the patients during the course of treatment with Ukrain. An interval of not less than

2 months since previous anticancer treatment preceded the application of Ukrain. Forty percent of the patients were given Ukrain as monotherapy.

The following characteristics were assessed at the beginning and at the end of each course of treatment: clinical manifestations, such as general status, appetite, sleep, intoxication signs, local pain, presence of tumor bleeding; data from hemograms and main biochemical examinations; and immunological status. This last included the following. (i) The number of T-cells in peripheral blood was determined by their capacity to form rosettes with three or more ram erythrocytes. (ii) The number of B-cells was determined by their capacity to form rosettes with three or more mouse erythrocytes. (iii) T-helpers/inductors (CD4) were evaluated in peripheral blood with the aid of monoclonal antibody IKO-86 (Scientific and Production Association "Medbiospectr," Moscow) by the peroxidase-antiperoxidase method, and T-suppressors/killers (CD-8) were evaluated with the aid of monoclonal antibody IKO-31. (iv) Natural killer cytotoxicity was determined with the aid of a radioimmune assay by leaving [³H]uridine out of K-562 target cells (human lymphosarcoma cells). (v) Immunoglobulins A, M, and G were determined in human sera by the radial immunodiffusion method: immune complexes were examined in human sera by precipitation in a 3.75% solution of polyethylene glycol 6000 and subsequent spectrophotometry, and oncomarkers (CEA, AFP, CA19-9) were determined by enzyme immunoassay (antibodies from Dia Plus, Switzerland). Comparative pathohistological investigation of tumor tissue by hematoxylin and eosin stains was performed in all cases except melanomas before and after the treatment. Statistical calculation of the data was made by Student's *t* test. Only statistically proved indexes are indicated ($P < 0.05$).

Probable unwanted local and general reactions to Ukrain were kept under observation during the course of treatment.

Results. Most of the patients who received Ukrain showed improvement of general status, decrease of fatigue, restoration of appetite, decrease of local pain intensity, and improvement of sleep after five to six injections (10 to 12 days from the beginning of the treatment).

Patients with rectum cancer noted decrease of rectal bleeding and decrease of local pain after treatment. Colostomy operation was postponed in two patients. Tumor nodes became softer and more movable. Resectable condition of a tumor was achieved in two cases. One of these tumors was removed. Another tumor was not removed, but we did not discover any metastases during a "second look" operation. Decrease of bleeding from tumor tissue after contact with coloscope, absence of ulceration, and coating of the place of prior biopsy with fibrin were revealed during a second biopsy. Patients with melanomas noticed improvement of general condition. Tumor nodules became softer.

We observed positive changes in hematological data (namely, increase of lymphocyte number and decrease of erythrocyte sedimentation rate) and normalization of immunological data as follows: increase of T-lymphocyte numbers, T-helpers, natural killer cytotoxicity, phagocyte activity, normalization of T-help to T-suppressor ratio, and appearance of large granular lymphocytes.

TABLE 1. Patient characteristics

Disease	Distribution	No. of patients
Cancer of rectum	T2 NX M0	1
	T3-4 N0 M0	4
	T2 N1 M0	1
	T3 N1 M0	1
	T3 NX M1	2
Cancer of stomach	T3 N1-2 M0	2
	T4 N1 M0	1
	T3 N2 M1	1
	T4 NX M1	1
Skin melanoma	T2 N2 M0	2
	T2 N2 M1	1
Soft tissue sarcoma	T3 N0 M0	2
	T3 NX M0	1
Cancer of uterus	T2 N1 M0	1
Cancer of gallbladder	T3 NX M1	1
Cancer of lungs	T2 NX M0	1

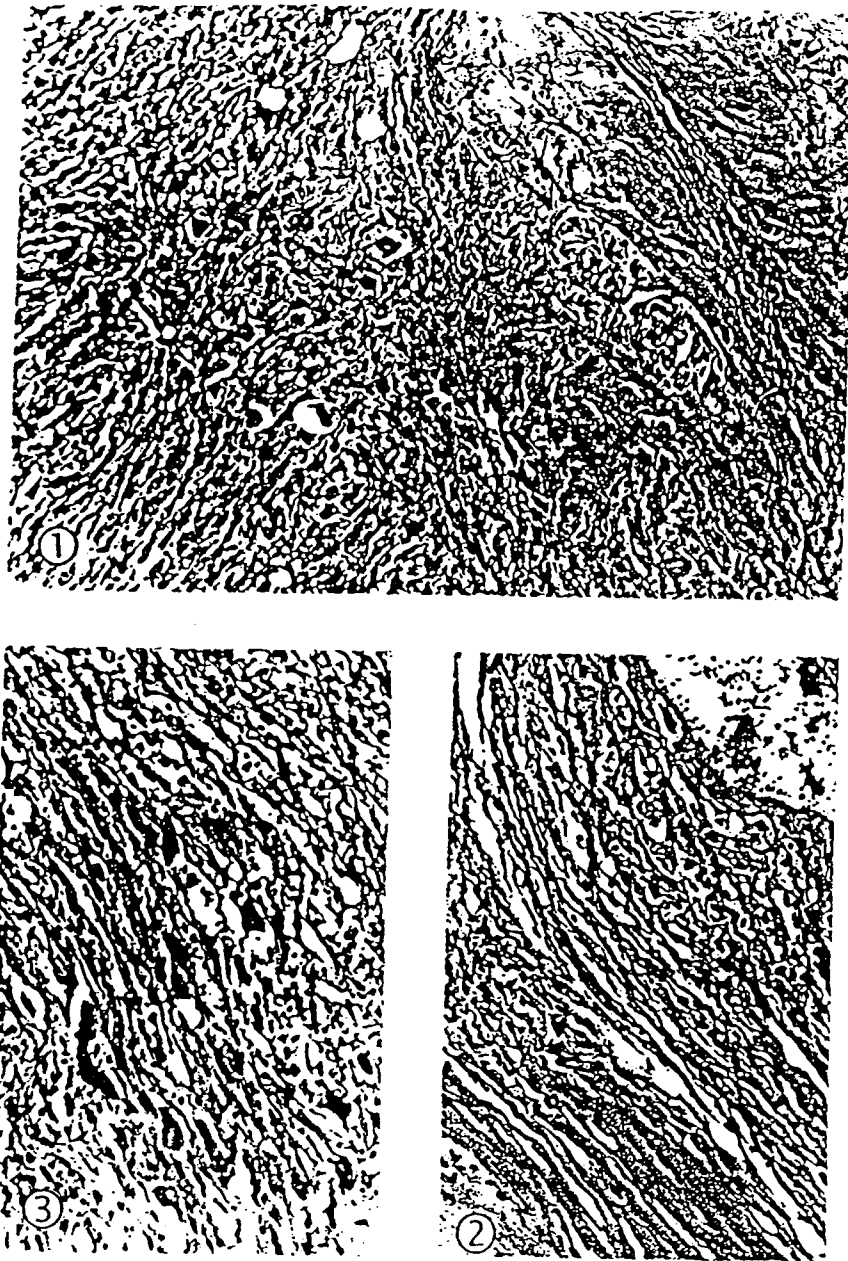


FIG. 1. Reduction of rhabdomyosarcoma after operation and Ukrain treatment. (1, 2) Strong connective tissue capsule around tumor; (2) absence of vascular and capsule invasion; (3) intensive lymphocytic infiltration of tumor tissue.

Decrease of titer of oncomarkers (CEA, AFP, CA19-9) took place in all cases. There were no negative changes in biochemical status. Pathomorphological data showed that in epithelial tumors treatment led to proliferation of stromal components and relative decrease of adenocarcinoma mass irrespective of histogenesis. Some lymphocytes were found at invasion borders. Sclerotisation of the stroma of adenocarcinomas was found in some cases.

Production of mature collagen was seen in stroma of the tumors in two cases of rectal cancer. Lymphocyte infiltration was seen over the whole tumor area. In sarcoma cases, increase of paravascular lymphocytes was revealed. Tumor cells became more monomorphic after treatment. Formation of alveolar and myofiber

structures and colchicine mitoses were noticed in one case of pleomorphic myosarcoma.

Proliferation and metastases of sarcomas during intervals between biopsies were not noticed. In one case of rhabdomyosarcoma of a thigh, formation of pseudocapsule around the relapsing tumor was found after treatment with Ukrain (Fig. 1).

Survival of patients after treatment with Ukrain of 6 to 10 months was 78%. Increase of metastases was noticed in one case of rectal cancer. In other cases there were no signs of metastases progression.

We observed neither general nor local unwanted reactions such as pain, allergy, or hyperthermy. Two patients had increasing body temperature up to 37.6°C during the first three injections but then temperature became normal.

Conclusion. This investigation confirmed the immunostimulating effects and cancerostatic abilities of the preparation Ukrain, as well as its atoxicity and good assimilation. Taking into consideration its properties, this preparation can be applied for treatment of advanced cancer patients which are inoperable and when there are no possibilities for application of traditional chemo- and radiotherapy. Use of this drug in ecologically unfavorable areas is very important. Further research of Ukrain is required, and undoubtedly it will be a good source of information about application of natural drugs in oncology.

The authors want to express their thanks and appreciation to everybody who helped in making this work a success.

1. Gordienko, S. M. 1990. Cell-bound immunity in people exposed to influence of radiation after the accident at the Chernobyl nuclear power station. Biological and radioecological aspects of consequences after the accident at the Chernobyl nuclear

power station. Theses, p. 207. First International Conference, Green Cape, September 10-18, 1990, Moscow.

2. Liepins, A. 1990. Enhancement of cell mediated lysis on tumor cell by Chelidonium majus L. alkaloids (Ukrain) *J. Cancer Res. Clin. Onc.* 116(Suppl. A3):118.10.

3. Liepins, A., and J. M. Nowicky. 1991. Ukrain is selectively cytostatic and cytotoxic to human tumor and HIV infected cell but not to human normal cell. *Recent Advances in Chemotherapy: Anticancer Section. Proc. 17th Intern. Conf. Chemoth. Berlin.* 2660.

4. Nowicky, J. M., et al. 1991. Evaluation of thiophosphoric acid alkaloid derivativ from Chelidonium majus L. (<Ukrain>) as an immunostimulant in patients w various carcinomas. *Drug Exp. Clin. Res.* 17:1339-1343.

5. Petrov, R. V., and G. V. Oradovskaya. 1990. Result of three-year immunologic monitoring after the contingent of persons taken part in a liquidation of consequences after the accident at the Chernobyl nuclear power station. Biological and radiological aspects of consequences after the accident at the Chernobyl nuclear power station. Theses, p. 206. First International Conference, Moscow.

6. Remiszewska, M., et al. 1992. Pharmacological effects of Ukrain in rats and rabbits. *Acta Pol. Pharm. Drug Res.* no. 5-6.

7. Serkiz, Ya. G., V. G. Pinchuk, and L. V. Pinchuk. 1992. Radiobiological aspects of the accident at the Chernobyl nuclear power station. Academy of Sciences of Ukraine. The Kavetsky R. G. Institute of Oncology and Radiobiology Problems. *Naukova Dumka*, p. 172.