

UKRAIN BOTH AS AN ANTI CANCER AND IMMUNOREGULATORY AGENT

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Summary: *Thirty six stage III cancer patients were treated with Ukrain, a semisynthetic drug derived from *Chelidonium majus* L. alkaloids conjugated with thiophosphoric acid. The drug was injected intravenously every second day in a dose of 10 mg per injection. Each patient received 300 mg of the drug (30 injections). The cytostatic effect of Ukrain was monitored clinically and by ultrasonography (USG) and computer tomography (CT), as well as by determination of CEA and CA-125 in the sera of patients with rectal and ovarian cancers, respectively. The influence of Ukrain on immune parameters was evaluated by monoclonal antibodies (MAb) to CD2, CD4, CD8 and CD22. The influence of Ukrain on immune parameters in cancer patients was matched with its effect on these parameters in 20 healthy volunteer controls. The results obtained indicate that Ukrain, in a concentration not cytostatic in normal cells, is cytostatic for malignant ones, and may suppress the growth of cancer. The compound also has immunoregulatory properties, regulating the T lymphocyte subsets.*

Introduction

Ukrain is a semisynthetic drug derived from *Chelidonium majus* L. alkaloids conjugated with thiophosphoric acid. The drug has unique properties such as a selective cytostatic effect on malignant human tumour cells, but not on normal cells (1, 2, 3). Furthermore, it has been found that the drug has an immunomodulating effect on the patient's immune system (4, 5, 6). The present studies were undertaken to confirm and extend the previous observations concerning both the anticancer efficacy of Ukrain and its immunomodulatory activity *in vivo*.

Patients and methods

The anticancer and immunomodulatory effects of Ukrain were evaluated in 36 patients with various malignancies including ovarian cancer (7 cases), rectal cancer (13 cases), breast cancer (8 cases), skin cancer (4 cases) and liver cancer (4 cases). All patients were in an advanced stage of disease (Stage III). The research protocols for Ukrain trials were approved by the ethics committees of the local Faculties of Medicine.

The influence of Ukrain on the growth of tumours was evaluated clinically as well as by ultrasonography (USG) and computer tomography (CT), and in patients with rectal and ovarian cancers by monitoring of CEA and CA-125 tumour markers,

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respectively. The influence of Ukrain on immunity was monitored by monoclonal antibodies (MAb) to CD2, CD4, CD8 and CD22 surface phenotypic markers. The influence of Ukrain on the synthesis of interleukin-1 was monitored in microcultures of peripheral blood monocytes. Twenty healthy volunteers formed a control group for immune parameters to cancerous patients.

Patients with malignancies, as well as the healthy subjects, were treated in the same way. They received 30 intravenous injections of the drug, each containing 10 mg of the compound, every second day. Therefore, each patient and each volunteer received 300 mg of the drug as total treatment. The blood for determination of immune parameters was collected from patients and healthy volunteers twice, before and at the end of treatment, and the same was done for determination of CEA and CA-125 in patients with ovarian and rectal cancers.

Results

Generally, patients injected with Ukrain tolerated it well. However, in some patients side effects were manifested by stabbing pains in the organs and/or tissues infiltrated by the neoplasm, hot flushes, fever, thirst and insomnia, lasting 24 h after injection. In patients with primary skin cancer and/or metastatic skin lesions, redness and pain in the invaded areas were observed. Some patients with rectal cancer exhibited, after Ukrain treatment, bleeding from the tumour undergoing necrobiosis.

The antimalignant effects of Ukrain on primary tumours and/or metastatic lesions were observed clinically, as well as by USG, CT and by monitoring CEA or CA-125 levels in the blood. Clinically, the primary tumours and metastatic lesions were decreased in several patients after treatment. However, the cytostatic effect of the compound was most pronounced on metastatic lesions in the liver, as seen by USG and/or CT. It was characterized by formation of necrotic foci with subsequent events due to re-

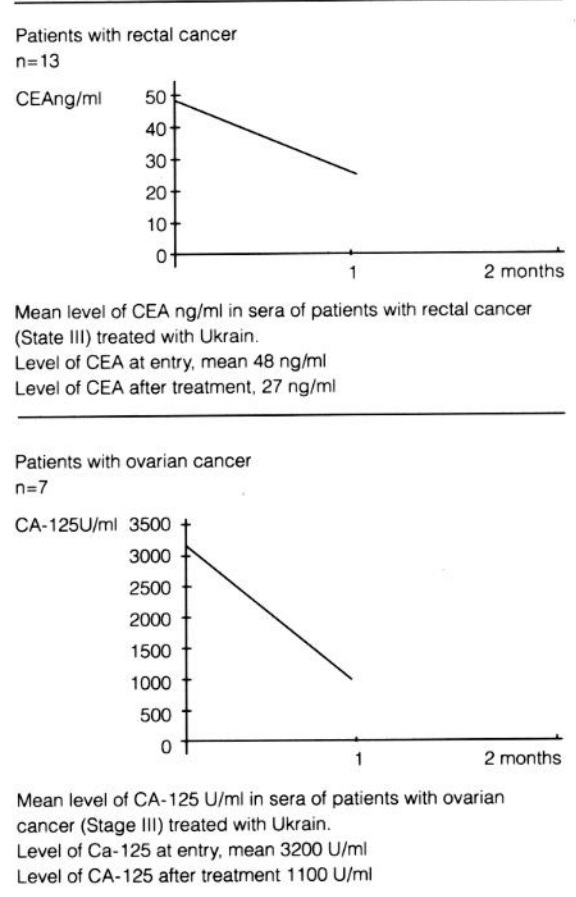


Fig. 1 Tumour markers in patients treated with Ukrain.

generation of the organ. As presented in Fig. 1, the cytostatic effect of the compound was also confirmed by a decrease in the level of CEA and CA-125 antigens. In these patients, the level of the markers dropped as much as threefold.

Immunologically, the effect of Ukrain on cancer patients was characterized by an increase of T cells with CD2, CD4 and CD8 phenotype markers (Table I). The data obtained from microculture studies that Ukrain enhances the production of interleukin-1 with

Table I Lymphocyte subpopulations in cancer patients and healthy subjects before and after treatment with Ukrain

Cancer patients n = 36										
CD2		CD4		CD8		CD4/CD8		CD22		
A	B	A	B	A	B	A	B	A	B	
41.3	61.2	25.6	38.9	15.6	27.5	1.64	1.41	20.1	18.6	
Healthy subjects n = 20										
CD2		CD4		CD8		CD4/CD8		CD22		
A	B	A	B	A	B	A	B	A	B	
68.5	70.1	38.7	42.2	19.5	21.8	1.98	1.93	20.1	18.9	

A – mean of presented parameters before treatment with Ukrain
B – mean of presented parameters after treatment with Ukrain

all regulatory consequences on functional parameters of immune cells.

Table I presents data identifying the influence of Ukrain on immune parameters in healthy subjects. As seen, this effect is minimal. As well as in cancer patients, in healthy volunteers T cells with CD2, CD4 and CD8 phenotype markers had increased. The effect was found to be proportional to the impaired immune parameters observed in the subject. According to clinical protocols injections of Ukrain to healthy volunteers did not cause any side effects similar to those observed in cancer patients.

Discussion

Considering that the patients described above were in a terminal stage of the disease and thus untreatable, it may be concluded that even in such persons Ukrain may be active and exert both cytostatic and immunotrophic properties. The anti tumour effect of Ukrain was confirmed by clinical observations as well as by USG and CT control procedures and by monitoring of CEA and CA-125

levels. After injections of the drug, decrease of the primary tumour size and/or its metastatic foci, decreased pain in the tumour or bleeding in patients with rectal cancer, and drop of CEA and CA-125 levels support the viewpoint that Ukrain is cytotoxic for tumour tissue.

The immunoregulatory effect of Ukrain may best be exemplified by the increase of T lymphocyte subsets and by regulation of CD4/CD8 index, as well as by data obtained from lymphocyte microcultures, indicative of increased synthesis of lymphokinin namely interleukin-1, in cancer patients as compared with normal healthy subjects. As shown in Fig. 1, in normal healthy subjects the immunoregulatory effect of Ukrain was seen only in those with some small impairment of immune parameters. Persons with normal immune parameters measured by MAB did not react to Ukrain treatment.

Of special interest is the observation that Ukrain, the antimalignant drug, injected in concentrations cytostatic for malignant cells, may be immunoregulatory for cells known to be very sensitive to chemotherapeutics. This phenomenon may best be explained by the difference in metabolic activities between normal and malignant cells. In consequence, a normal cell is able to metabolize Ukrain, contrary to malignant cells for which Ukrain is even deadly. This viewpoint seems to be supported by the recent observations of Hohenwarter *et al.* (7) who found, in *in vitro studies*, Ukrain in much higher concentration in malignant cells than in normal cell cultures.

These data all indicate that Ukrain may be considered as an alternative anticancer compound which may be useful in the oncologic clinic.

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