

# RECENT ADVANCES IN CHEMOTHERAPY

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## Immunological and Tumoricidal Properties of Ukrain

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Ukrain is a semisynthetic compound from *Chelidonium majus* L. alkaloids and thiophosphoric acid. Chemically it is 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]phenanthridinium-6-o)-ethane-aminyl]phosphinesulfide · 6HCl. It shows malignotoxic and immune stimulating properties (1). Being toxic to cancer cells in a range of about  $10^{-4}$  mol, it shows no toxic properties to normal cells in even 100-fold-higher concentration (2-4). 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. Thirty-two healthy volunteers (25 to 55 years; 16 females and 16 males) were treated with Ukrain according to the same schema. In contrast to the oncological patients, no significant changes in T lymphocyte subsets of the healthy volunteers could be induced by Ukrain.

**Methods.** Fifty-one patients were in advanced stage of disease (stage III). The malignancies included ovarian cancer ( $n = 12$ ), rectal cancer ( $n = 18$ ), breast cancer ( $n = 12$ ), skin cancer ( $n = 5$ ) and liver cancer ( $n = 4$ ) and no further treatment was to be undertaken. Laboratory data were available as for the healthy volunteers and included special oncological tests (CA, Ca-125). Thirty-two healthy volunteers were used as controls in immunological parameter changes. Their states of health were established on the basis of their medical histories, physical examinations, and subsequent laboratory investigations: ESR, morphology, blood smears, urine, bilirubin, glutamic oxaloacetic transaminase, GPT, blood urea nitrogen, creatine, uric acid, cholesterol, chest X ray, ECG, and ultrasonographic, surgical, and gynecological consultations.

The influence of Ukrain on the growth of tumors was evaluated clinically by ultrasonography and computer tomography in patients with rectal and ovarian cancers by monitoring the CEA and CA-125 oncogenic markers. The influence of Ukrain on immunological parameters was monitored by monoclonal antibodies to  $T_2$ ,  $T_4$ ,  $T_8$ , and  $T_{22}$  surface phenotypic markers. Treatment with Ukrain was 30 intravenous injections, each containing 10 mg every second day for patients and volunteers. Blood was taken before and at the end of the treatment for tumor marker and immunological analyses.

**Results.** Ukrain was generally well tolerated. However, in some patients side effects were manifested by stabbing pains in the regions of tumor and/or metastases. Hot flushes, fever, thirst, and insomnia, lasting about 24 h after injection, were also seen. A few patients with rectal cancer exhibited bleeding from the tumor undergoing necrobiosis after Ukrain treatment. The antimalignant effects of Ukrain could be demonstrated by ultrasonography and computer tomography by decreases in the primary tumor and/or metastatic lesions in several patients. This cytostatic effect was most pronounced on metastatic lesions in the liver. It was characterized by formation of necrotic foci with subsequent events due to regeneration of the organ. The cytostatic effect of Ukrain was also confirmed by a decrease in the levels of CEA and CA-125 antigens (Fig. 1).

Immunologically, the effect of Ukrain on cancer patients was characterized by an increase of T cells with  $T_2$ ,  $T_4$ , and  $T_8$  phenotypic markers (Fig. 2). Immunologically, the effect of Ukrain on healthy volunteers was negligible (Fig. 3). Spasmodic and chologogic actions of the preparation were found in two volunteers. It is worth emphasizing that during the period of Ukrain application numerous catarrhal and parainfluenza infections were prevalent at the place of treatment. However, no such infections were observed

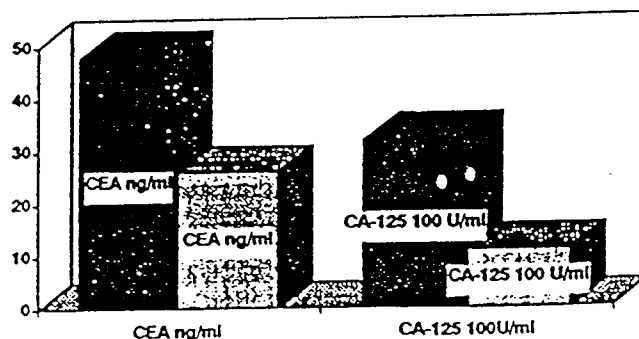


FIG. 1. Antibody levels in patients with rectal cancer and patients with ovarian cancer before (dark boxes) and after (light boxes) treatment with Ukrain.

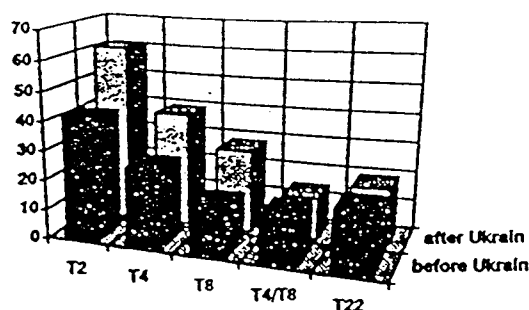


FIG. 2. Lymphocyte subpopulations in cancer patients before and after treatment with Ukrain.

in any of the volunteers taking Ukrain. There were no harmful side effects. After administration all volunteers were in good or even better general states of health.

**Discussion.** Considering the fact 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 immunotropic properties.

The antitumor effect of Ukrain was confirmed by clinical observations as well as by ultrasonography and computer tomography and by monitoring of CEA and CA-125 levels. A decrease of primary tumor size and/or its metastatic foci, decreased pains in the tumor, and a drop of CEA and CA-125 levels support the viewpoint that Ukrain is cytotoxic to tumor tissue. Immunoregulatory effects are exemplified by the increase of T-lymphocyte subsets. It is of interest that Ukrain given in concentrations

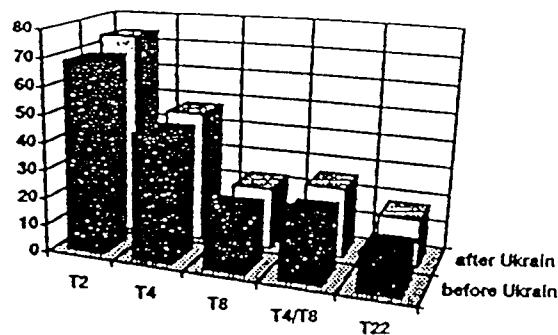


FIG. 3. Influence of Ukrain on the immune parameters in healthy volunteers.

that are cytostatic for malignant cells may be immunoregulatory for cells known to be very sensitive to chemotherapeutic. Ukrain may therefore be considered as a powerful alternative anticancer compound in the oncologic clinic. Ukrain shows no adverse effects in healthy volunteers.

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