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# RETROSPECTIVE STUDY OF UKRAIN TREATMENT IN 203 PATIENTS WITH ADVANCED-STAGE TUMORS

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**Summary:** *A total of 203 advanced-stage cancer patients suffering from different types of cancer who had exhausted all conventional forms of therapy were treated with the novel antitumor drug Ukrain over a period of 2.5 years at the Villa Medica Clinic in Germany. Seventy-six patients (37.4%) were simultaneously treated with regional deep hyperthermia in which tumor tissue was heated to >42.5 °C. Patients also received complementary oncological treatment with selen, cimetidine, thyme extract and vitamin A. In view of the advanced stage of the disease, the results of therapy were surprising. Forty-one patients (20.2%) achieved total remission, 122 (60.1%) partial remission and only 40 (19.7%) did not respond to treatment. The highest response rates were in patients with seminoma (three out of four patients had total remission and one had partial remission) and in prostate cancer [14 out of 20 patients (70%) achieved total remissions and five achieved partial remission].*

## Introduction

Ukrain is a semisynthetic compound from the alkaloids of *Chelidonium majus L.* and thiophosphoric acid triaziridide, which has already been shown to have considerable promise in the treatment of a variety of oncological diseases (1-5). Although its mechanism of action has not yet been elucidated, it has been demonstrated to attack cancer cells while leaving healthy cells undamaged (6). The drug's antitumor effect is developed through a dose-correlated inhibition of DNA, RNA and protein synthesis (5, 7).

*In vitro* tests at the National Cancer Institute (Bethesda, USA) showed Ukrain (NSC-631570) to be effective and malignocytolytic against all human cancer cell lines tested, whereas 5-fluorouracil (NSC-19893) did not reduce tumor cell mass but only inhibited the growth of malignant cell lines (8). Ukrain has been shown to induce apoptosis (programmed cell death) in malignant cells (9).

Ukrain is known to correct the immune response of patients, especially T-cell mediated response as well as enhanced cell-mediated cytotoxicity with an increase in the T lymphocyte count and normalization of the T helper/T suppressor ratio (10).

## Patients and methods

A total 203 patients suffering from various types of advanced stage cancer were treated with Ukrain

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between August 1997 and the end of 1999. Their diseases had been treated with all the conventional methods and because of recidivation and/or progress, no further therapy modality was available to them. These patients had exhausted all therapy options.

The preconditions for such therapy are laid down under German medical law (number 73, clause 3 AMG). In essence, they require that: i) conventional methods of treatment are not available or no longer available; ii) it can be proved that patients have exhausted all therapy options; iii) the Karnofsky index is recognizably >50%; and iv) life expectancy is more than 4 weeks.

Patients received Ukrain (Norwicky Pharma, Vienna, Austria) at a dose of 0.3 mg/kg b.w., 3 times per week for 3 weeks. The drug was administered with a standardized 250 ml 5% glucose infusion solution with the addition of vitamin C (Pascoe, Giessen, Germany) at 0.3 g/kg b.w. Seventy-six patients also received regional deep hyperthermia in which tumor tissue was heated to a temperature of >42.5 °C. After immune phenotyping the patients received accompanying complementary oncological treatment with selen (Biosyn, Fellbach, Germany), cimetidin (ct-Arzneimittel, Berlin, Germany), thyme extract (Dr. Aschoff, Edenkoben, Germany) and vitamin A (Jenapharm, Jena, Germany).

The 203 patients had a mean age of 46.3 years (22 months to 74 years). There were 14 children below the age of 16 (8 girls and 6 boys) and 189 adults (107 women and 82 men). Seventy-six (37.4%) were simultaneously treated with regional deep hyperthermia in treatment cycles of 3 weeks with a 3-4 week pause between cycles. Patients underwent 1-15 cycles (average 2.6 cycles).

The most common form of cancer was colorectal (31 patients), followed by breast cancer (25 patients) and prostate cancer (20 patients).

## Results

Ukrain was generally well tolerated. Typical adverse effects were temperature increases of up to 2-3 °C, feelings of warmth, stabbing pains, itching and tingling sensations at the sites of tumors or metastases. Some patients reported feelings of nausea after the first Ukrain injection but not after subsequent injections. Three patients presented skin rash. All these adverse effects disappeared spontaneously and none required medication or additional therapy. Interruption of Ukrain therapy as a result of adverse effects was not indicated in any of the patients.

These adverse effects appeared in patients who responded to therapy and disappeared as the tumor mass became smaller. It can therefore be concluded that they were caused by the influence of tumor degradation products rather than by Ukrain itself.

Of the 203 patients treated with Ukrain, 41 (20.2%) achieved full remission, 122 (60.1%) partial remission and only 40 (19.7%) did not respond to treatment. Full remission was achieved in three out of four patients with seminoma and in 14 out of 20 patients (70%) with prostate cancer. Exceptionally high percentages of full remission were also achieved with neuroblastoma (60%), Ewing's sarcoma (57.1%) and astrocytoma (33.3%). High percentages of partial remissions were achieved with colorectal cancer (22 patients, 71%), breast cancer (16 patients, 64%), small-cell lung cancer (6 patients, 75%) pancreas cancer (6 patients, 85.7%) and gall bladder cancer (6 patients, 100%).

Total or partial remissions were achieved by 163 (80.3%) of the 203 patients treated. A full list of results is shown in Table I.

Immune phenotyping before and 3-5 days after each treatment cycle showed that on average the lymphocyte count increased by 122%, total T lymphocytes by 87.2% and natural killer cells by 87.2%. Total CD4 lymphocytes increased by 113% and total activated CD4 lymphocytes by 98.2%. The greatest

**Table I** *Results of Ukrain therapy in 203 patients with various advanced-stage cancers*

| Type of tumor (according to frequency) | | Number | Full remission | | Partial remission | | No influence | |
|---|---|---|---|---|---|---|---|---|
| | | | Number | % | Number | % | Number | % |
| 1 | Colorectal cancer | 31 | 5 | 16.1 | 22 | 71 | 4 | 12.9 |
| 2 | Breast cancer | 25 | 7 | 28 | 16 | 64 | 2 | 8 |
| 3 | Prostate cancer | 20 | 14 | 70 | 5 | 25 | 1 | 5 |
| 4 | Small-cell lung cancer | 8 | 1 | 12.5 | 6 | 75 | 1 | 12.5 |
| 5 | Ewing's sarcoma | 7 | 4 | 57.1 | 3 | 42.9 | | |
| 6 | Osteogenic sarcoma | 7 | | | 5 | 71.5 | 2 | 28.5 |
| 7 | Signet ring-cell cancer | 7 | | | 6 | 85.7 | 1 | 14.3 |
| 8 | Pancreas cancer | 7 | | | 6 | 85.7 | 1 | 14.3 |
| 9 | Stomach cancer | 6 | 1 | 16.6 | 4 | 66.6 | 1 | 16.6 |
| 10 | Squamous cell cancer | 6 | | | 5 | 83.3 | 1 | 16.6 |
| 11 | Gall bladder cancer | 6 | | | 6 | 100 | | |
| 12 | Neuroblastoma | 5 | 3 | 60 | 1 | 20 | 1 | 20 |
| 13 | Ovarian cancer | 5 | 1 | 20 | 4 | 80 | | |
| 14 | Seminoma | 4 | 3 | 75 | 1 | 25 | | |
| 15 | Nephroblastoma | 4 | | | 1 | 25 | 3 | 75 |
| 16 | Glioblastoma | 4 | | | 3 | 75 | 1 | 25 |
| 17 | Lung adeno cancer | 4 | | | 2 | 50 | 2 | 50 |
| 18 | Vulva-cervical cancer | 4 | | | 4 | 100 | | |
| 19 | Malignant melanoma | 4 | | | 3 | 75 | 1 | 25 |
| 20 | Astrocytoma | 3 | 1 | 33.3 | 1 | 33.3 | 1 | 33.3 |
| 21 | Unknown genesis | 3 | 1 | 33.3 | 2 | 66.6 | | |
| 22 | Rhabdomyo sarcoma | 3 | | | 1 | 33.3 | 2 | 66.6 |
| 23 | Medulloblastoma | 3 | | | 2 | 66.6 | 1 | 33.3 |
| 24 | Non-Hodgkin's lymphoma | 3 | | | 2 | 66.6 | 1 | 33.3 |
| 25 | Pleura-mesothelioma | 2 | | | 2 | 66.6 | | |
| 26 | Appendix cancer | 2 | | | 2 | | | |
| 27 | Mesothelioma | 2 | | | 1 | | 1 | |
| 28 | Kidney cell cancer | 2 | | | 1 | | 1 | |
| 29 | Soft-tissue tumor or origin | 2 | | | 1 | | 1 | |
| 30 | Epidermoid bronchial cancer | 1 | | | 1 | | | |
| 31 | Hepatocellular cancer | 1 | | | 1 | | | |
| 32 | Lymphoepithelial nasopharyngeal cancer | 1 | | | 1 | | | |
| 33 | Bladder cancer | 1 | | | 1 | | | |
| 34 | Klutskin tumor | 1 | | | 1 | | | |
| 35 | Nephroblastoma | 1 | | | | | 1 | |
| 36 | Leydig cell tumor | 1 | | | | | 1 | |
| 37 | Leyemyo sarcoma | 1 | | | | | 1 | |
| 38 | Neuroectodermal tumor | 1 | | | | | 1 | |
| 39 | Histiocytoma | 1 | | | | | 1 | |
| 40 | Mucoepidermoid cancer | 1 | | | | | 1 | |
| 41 | Peritoneal soft-tissue cancer | 1 | | | | | 1 | |
| 42 | Schwannoma | 1 | | | | | 1 | |
| 43 | Ependymoma | 1 | | | | | 1 | |
| 44 | Neuroectodermal tumor | 1 | | | | | 1 | |
| | Total | 203 | 41 | 20.2 | 122 | 60.1 | 40 | 19.7 |

improvements were measured after the first treatment cycle; as immune values came within the normal range changes were less pronounced. This suggests that Ukrain acts as an immunocorrector.

Patients who responded to Ukrain therapy showed an improvement in their general condition, with reduced pain, increased appetite, increased vitality, a more positive attitude and normalization of sleep patterns.

In cases of bone metastases it was observed that although Ukrain alone had very little effect and deep hyperthermia had none, in combination they exerted a strong influence.

## Discussion

These results of Ukrain therapy are outstanding, especially in view of the fact that these patients had exhausted all conventional forms of cancer therapy. In addition, the drug brought clear therapeutic benefits for tumor types, such as prostate cancer, pancreas cancer and colorectal cancer, for which there is currently no satisfactory treatment. The results of this study indicate that further research into Ukrain should be focused on seminoma, prostate cancer, neuroblastoma, Ewing's sarcoma, astrocytoma, breast cancer, ovarian cancer, stomach cancer, colorectal cancer and small-cell lung carcinoma.

The improvement in immune status brought about by Ukrain is also noteworthy. The greatest changes occurred in patients whose immune systems were most damaged. As immune levels returned within the normal range the influence of Ukrain was reduced, leading to the conclusion that the drug is an immunocorrector.

In view of these surprising results, the question arises as to what the effect of Ukrain would have been if administered in the early stages of the disease. Further studies are urgently needed to establish in which areas and to what extent this promising anticancer drug could be used for the benefit of cancer sufferers.

## References

(1) Vatanasapt V., Wongpratoom W., Mairiang P., et al. *Preliminary report on clinical experience in the use of Ukrain.* Thai Cancer J., **17** (1-2), 20, 1991.

(2) Musianowycz J., Judmajer F., Manfreda D., et al. *Clinical studies of Ukrain in terminal cancer patients (phase II).* Drugs Exptl. Clin. Res., **18**, 45, 1992.

(3) Staniszewski A., Slesak B., Kolodziej J., Harlozinska-Smyrka A., Nowicky J.W. *Lymphocyte subsets in patients with lung cancer treated with thiophosphoric acid alkaloid derivatives from Chelidonium majus L. (Ukrain).* Drugs Exptl. Clin. Res., **18**, 63, 1992.

(4) Bondar G., Borota A., Yakovets Y., Zolotukhin S. *Comparative evaluation of the complex treatment of rectal cancer patients (chemotherapy and X-ray therapy, Ukrain monotherapy).* Drugs Exptl. Clin. Res., **24** (5/6), 221, 1998.

(5) Uglyanitsa K., Nefyodov L., Nowicky J.W., Brzosko W. *The effect of Ukrain on cancer of the urinary bladder.* 17th Int. Cancer Cong., Rio de Janeiro, 24-28 August, 1998, pp. 1065-1068.

(6) Liepins A., Nowicky J.W. *Ukrain is selectively cytostatic and/or cytotoxic to human tumour and HIV-infected cells but not to normal human cells.* Proc. 17th Int. Cong. Chemother, Berlin, 1991, Abst. 163, pp. 2660-2261.

(7) Nowicky J.W., Greif M., Hamler F., Hiesmayr W., Staub W. *Macroscopic UV-marking through affinity.* J. Tumour Marker Oncol., **33**, 4, 1988.

(8) Nowicky J.W., Hiesmayr W., Nowicky W., Liepins A. *Influence of Ukrain on human xenografts in vitro.* Drugs Exptl. Clin. Res., **22** (Suppl.), 93, 1996.

(9) Liepins A., Nowicky J.W., Bustamante J.O., Lam E. *Induction of bimodal programmed cell death in malignant cells by the derivative Ukrain (NSC-631570).* Drugs Exptl. Clin. Res., **22** (Suppl.), 73, 1996.

(10) Nowicky J.W., Staniszewski A., Zbroja-Sontag W., Sesak B., Nowicky W., Hiesmayr W. *Evaluation of thiophosphoric acid alkaloid derivatives from Chelidonium majus L. ('Ukrain') as an immunostimulant in patients with various carcinomas.* Drugs Exptl. Clin. Res., **22** (2), 139, 1991.