

## **New anticancer drug**

# **UKRAIN**

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### **BACKGROUND**

Greater celandine (*Chelidonium majus L.*) is well known in herbal medicine since more than 3,000 years. The latex of greater celandine has been used mostly to treat skin warts. However, internal use of celandine is strongly limited due its high toxicity. By means of a patent processing method a product was developed which can be administered intravenously and has affinity to cancer cells. The inventor named this product Ukrain after his country of birth.

### **REGULATORY STATUS**

This drug has been approved as standard anticancer medication in United Arab Emirates (registration no. 4987-6179-1), some countries of Europe (for example, Ukraine: first approval on October 18, 1998, #3641, re-approval on September 2, 2003, #3641), Mexico (No. 036M2005 SSA). Ukrain has also been designated as an Orphan Drug for pancreatic cancer in the USA (Designation Request #03-1693) and also in Australia (File 004/009839). Ukrain has been presented 264 times at international scientific congresses and symposia as for example International Congresses of Chemotherapy, Annual Meetings of the American Association for Cancer Research, NCI – EORTC Symposium on New Drugs in Cancer Therapy and many others. 1997, at the 20<sup>th</sup> International Congress on Chemotherapy in Sydney, Australia, a whole sectional meeting was devoted to UKRAIN. Ukrain has been subject of 257 research publications.

### **PROPERTIES AND MECHANISM OF ACTION**

Ukrain is the first and only anticancer drug accumulating during minutes after administration in cancer cells (slide 1-3). Because it triggers apoptosis in cancer cells (slide 4) this drug is only toxic against cancer cells while, in contrast to chemotherapy, at therapeutic dose it leaves healthy cells undamaged (slide 5, slide FU).

Through its antiangiogenic properties this medicine encapsulates tumours, thereby making them accessible to surgery (slides 6-7).

Ukrain has a unique mechanism of action that is definitively different from other medicinal products. In short, Ukrain induces apoptosis of cancer cells by inhibition of the polymerisation of tubulin; this results in a stop of cell growth in the G2M-phase. This

mechanism is clearly different from that of gemcitabine (an analogon of pyrimidine; instead of cytidine, gemcitabine-triphosphate is build into the DNA-helix and DNA-synthesis stops) as well as of erlotinib (which is a selective inhibitor of tyrosine-kinase; cell growth is stopped by blocking the transmission of growth signals via the human epidermal growth factor receptor). Ukrain has therefore an innovative mechanism of action, different of the action of these two medicinal products.

In addition, this preparation has an immune-modulating effect (slide 8 kiss), whereby it improves the general condition of patients and does not only prolong their lives but in many cases also affects a recovery (slide 9, breast cancer).

Due to its therapeutic index (ratio of therapeutic dose to the toxic one) of 1250 – on contrary to common cytostatics with TI of 1.4-1.8, the dose range which has been toxic to cancer cells had no noxious effects on the patient's body. Probably this is the reason why Ukrain does not provoke necroses when being administered intramuscularly as well. This unique capacity has been proven in many studies by researchers from various countries with, in total, 16 malignant and 9 normal cell lines:

- Hohenwarter et al, 1992: human osteosarcoma and melanoma cell lines; human endothelial cells from umbilical vein.
- Cordes et al, 2002: human tumor cell lines MDA-MB-231 (breast), PA-TU-8902 (pancreas), CCL-221 (colorectal), U-138MG (glioblastoma); human skin and lung fibroblastic cells HSF1, HSF2 and CCD32-LU.
- Roublevskaia et al, 2000 (Anticancer Research): ME180 and A431 carcinoma cell lines; HaCaT normal human keratinocytes.
- Gagliano et al, 2007: glioblastoma MI cell lines T60, T63 and glioblastoma.
- Habermehl et al, 2006: Jurkat A3 T-lymphoma, caspase-9 DN expressing Jurkat, caspase-8 and FADD negative Jurkat, CD95/TRAIL-resistant Jurkat A3, and Bcl-2 overexpressing Jurkat cells; Jurkat J16 control cells, cFLIP-L expressing Jurkat cells.
- Panzer et al, 1998: HeLa human cervical carcinoma and Hs27 (human foreskin fibroblasts), WHCO5 (squamous oesophageal cancer); Graham 293 (transformed human embryonic kidney) and Vero (transformed African green monkey kidney).

229 scientists from 22 countries at 58 research institutions and state universities worked extensively on the effects of Ukrain. This agent has been revealed to inhibit tubulin polymerisation (Panzer 1998, Ramadani 2000), to cause the cell cycle arrest of cancer cells in G2/M phase with cyclin CDK1 and CDK2 upregulation (Roublevskaia et al, 2000) with selective apoptosis induction in cancer cells (Lanvers-Kaminsky et al, 2006) through mitochondrial caspases activation (Habermehl et al, 2006) in intrinsic cell death pathway (Mendoza et al, 2006). Ukrain caused also downregulation of metalloproteinases expression (Gagliano et al, 2006).

Many preclinical studies have proven the efficacy of Ukrain against various human cancer cell lines, including cisplatin-resistant cell lines. One of the most important of these studies - the research at the National Cancer Institute (Bethesda, Maryland, USA) where Ukrain was tested on the screening panel with 60 cell lines from eight human cancer types and revealed to be malignotoxic (toxic for cancer cells) against all the solid cancer cell lines tested. As the common anticancer drugs are toxic both

against cancer and normal cells they are named cytostatics – Ukrain, on the contrary, is toxic only against cancer cells and therefore is named malignocytolytic drug.

These preclinical results were then confirmed in randomised and controlled clinical studies as well as in many clinical observations on various malignant tumours like pancreas, colorectal cancer, prostate, lung, breast, ovarian, stomach cancer, melanoma and others.

## **PANCREAS CANCER**

As world leading expert in pancreas carcinoma treatment Prof. H.G. Beger of the Ulm University, Germany, author of 21 books and more than 600 scientific publications was unsatisfied with the results of the therapy in this very aggressive cancer, he was looking for new therapy modalities. Prof. Beger paid attention on the medicine Ukrain and started *in vitro* tests. In the tests with pancreas cancer cell lines Jurkat, MiaPaCa2, AsPC1, BxPC3 und THP-1 the researchers of Prof. Beger's group revealed Ukrain has a strong malignocytolytic effects on these cell lines. The mitotic analysis revealed mitotic arrest of cancer cells in the prophase and/or metaphase. This was a very important study to clarify the exact mechanism of action of Ukrain.

After the researchers from the University of Ulm have proved *in vitro* the efficacy of Ukrain against pancreas cancer cell lines and revealed the mechanism of action of Ukrain, Prof. Beger reviewed preclinical toxicity data, ascertained the safety of the drug and performed a pilot clinical trial

In this study 90 patients with histologically verified inoperable pancreatic cancer were treated in a controlled, randomised study at the University of Ulm (Germany). Patients in Group A received the standard chemotherapeutic drug Gemcitabine 1000 mg/m<sup>2</sup> body area, those in Group B received 20 mg UKRAIN, and those in Group C received 1000 mg/m<sup>2</sup> Gemcitabine followed by 20 mg UKRAIN per week. Survival rates after 6 months were 26% in the gemcitabine group, 65% in Ukrain Group B and 74% in the combination Group. The results showed that in inoperable advanced pancreatic cancer, survival rates were doubled using UKRAIN in combination with gemcitabine.

The recent clinical study by Gansauge et al, 2007 provided additional data on the benefit of a combined, adjuvant treatment with Ukrain and gemcitabine. The relapse-free survival time was 21.7 months, and median survival 33.8 months compared to 20.4 months (Kurosaki et al, 2004), what is clearly better compared to the literature. The actuarial survival rates were 86.7% after one year, 76.6% after two years, 46.7% after three years and 23.3% after five years (these patients are still alive).

Again, this publication supports the efficacy (and safety) of the use of Ukrain as it demonstrates a considerable prolongation of survival compared to what is known from literature.

Patients in the study by Gansauge et al, 2002 on palliative treatment of pancreas cancer were further observed after the conclusion of the study and it was noted that UKRAIN was well tolerated and could be administered without complications to all

patients. UKRAIN brought about a significant increase in survival time in comparison to therapy with Gemcitabine alone. Combination therapy with Gemcitabine and UKRAIN showed no advantage over monotherapy with UKRAIN. In the gemcitabine group the longest survival was 19 months, in the combination group 26 months, whereas in the Ukrain alone group three patients lived longer than 28 months and were still alive at the time of publication.

As a consequence of the results of this study the doctors from the University of Ulm recommend UKRAIN monotherapy in the palliative treatment of advanced pancreatic cancer – one of the most aggressive and resistant to treatment.

In another study by Prof. Zemskov et al. (National Medical University Kiev, Ukraine) 42 patients with pathologically verified pancreatic cancer were randomly enrolled in either of two groups: one group received vitamin C plus UKRAIN, the control group vitamin C plus best supportive care. The UKRAIN therapy dose was 10 mg intravenously every second day, to a total of 100 mg per patient. The survival rate after one year was 76% in the group treated with UKRAIN as opposed to 9.5% in the control group. The survival rate after two years was 48% in the UKRAIN-treated group with the longest survival of 70 months, and 5% in the control group. This study confirmed that best results can be achieved with Ukrain monotherapy.

A total of 28 patients with pancreatic adenocarcinoma were treated with Ukrain between August 1997 and December 2003 in the clinic Villa Medica, Germany. All the patients presented with advanced and/or metastatic disease that made curable radical surgery impossible. Twenty-one patients had previously been treated with 5-fluorouracil or gemcitabine, but due to disease progression this therapy was discontinued. Seven patients rejected conventional chemotherapy. Ukrain was administered at a dose of 20 mg three times a week for the first three months and then at a dose of 20 mg once a week for 4 months (total dose: 320 mg). Ukrain was generally well tolerated. Partial remission was achieved in 24 cases (85.7%) while four patients (14.3%) did not respond to treatment. Twenty-four patients described their quality of life during Ukrain treatment as “good”, and all the patients noted improvement in their general condition after treatment with Ukrain. The mean survival of the patients treated with Ukrain was 26.1 months.

These results demonstrate efficacy of Ukrain against one of the most aggressive and resistant cancer. This action observed both *in vitro* and in clinic. This is the reason for wide efficacy of this drug in various tumors.

## **COLORECTAL CANCER**

In the *in vitro* screening program of National Cancer Institute in Bethesda, USA, the effect of Ukrain (NSC 631570) on colon cancer cell lines among other was examined (slide ...). UKRAIN showed a pronounced growth-inhibiting effect in colorectal cancer cell lines, which in higher concentrations developed into a cytolytic effect leading to a reduction in cell biomass. 5-Fluorouracil, the standard chemotherapeutic agent to treat colon cancer actually, (5-FU, ascribed code: NSC 19893) was examined under identical conditions and the dose-response curves for 5-FU showed inhibition only in 8 human colon cancer cell lines in a  $10^{-3.5}$  molar sample concentration, which is 10 times higher than the

concentration of Ukrain. No lethal effects could be achieved with 5-FU on human colon cancer cells with this method; nevertheless the NCI judged that the anticancer activity of this compound was outstanding. The dose-effect plots of 5-fluorouracil were much flatter than those for Ukrain, and only in single cases and extremely high doses, displayed complete growth inhibition but not malignocytolytic effect as in the case of Ukrain (slide ). In this study Ukrain confirmed its malignocytolytic effect.

These promising results found confirmation in two randomised clinical trials. 96 patients with colorectal carcinomas were included in a randomised study conducted by Prof. Susak and Prof. Zemskov (National Medical University Kiev, Ukraine). 48 patients were treated with UKRAIN (15 of them with metastasising and 33 with non-metastasising colorectal tumours) and 48 patients were treated with the chemotherapeutic drug 5-FU and radiotherapy. The survival rate after 21 months was 78% in the group treated with UKRAIN and 33% in the group treated with 5-FU and radiotherapy.

In another trial, 48 patients with rectal carcinomas participated in a randomised study carried out by Acad. Bondar and Prof. Borota (Regional Cancer Centre, Donetsk Medical University, Ukraine). 24 patients received high-dosage radiotherapy and a therapy series with 5-FU before the operation, and another 24 patients received one series of UKRAIN therapy before the operation (10 mg every second day, to a total of 60 mg) and one series after the operation (to a total of 40 mg). During the following 14 months, 25% of patients who had received 5-FU and radiotherapy had relapses but only 8.3% of patients who had received UKRAIN. In the two years after this, 33.3% of patients who had received 5-FU and radiotherapy had relapses but only 16.7% of the patients who had been treated with UKRAIN.

## PROSTATE CANCER

The effect of Ukrain on the prostate cancer has been studied by several research groups *in vitro*. The group from Rochester University, USA used the cell line LNCaP. Ukrain induced morphological changes with cells becoming elongated and spindle shaped. Flow cytometry revealed a dose-dependent increase in the number of apoptotic cells. At 3.5  $\mu$ M, Ukrain treatment resulted 73% of cells G<sub>2</sub>/M-phase compared to 10% of control cells. Although the number of cells in G<sub>2</sub>/M-phase decreased with increasing dose, the number of apoptotic cells increased. UKRAIN was found to up-regulate the expression of the cyclin-dependent kinase inhibitor, p27 (Roublevskaia et al., 2000).

This malignocytolytic effect was confirmed in clinic. 74 patients with prostatic carcinoma were involved in a controlled study at the Villa Medica Clinic (Edenkoben, Germany). These patients had already been treated according to all conventional therapy protocols, and due to relapse and/or progression of the disease had no further conventional options available. They were treated with UKRAIN, and partially at the same time with local hyperthermia, and the following results were obtained: complete remission (full tumor disappearance) in 73% of patients and partial remission (partial tumor disappearance) in 22%, with only 5% of patients showing no effect on the progress of the disease (slide ...). Many physicians also observed tumor remissions after the out-patient treatment of prostate cancer.

## BREAST CANCER

The effect of Ukrain on breast cancer has been studied *in vitro* on the cell line MDA-MB-231 (Cordes et al, 2002) and *in vivo* as well.

In a study from Miami University, USA, BALB/C mice (15 animals) received subcutaneous injection of transplantable rapid growth mammary adenocarcinoma (D1 DMBA-3). On day 14, in the group receiving intravenous treatment with Ukrain, tumour growth had slowed down significantly ( $p < 0.05$ ). These data indicate that *in vivo* effects of Ukrain against the development of mammary tumours may be due, at least in part, to its ability to restore macrophage cytolytic function (Sotomayor et al., 1992).

75 patients with breast cancer (clinical stages I, II, III, T1-3N0-2M0, ages up to 70 years) were the subject of a controlled clinical study conducted at the University Grodno (Belarus). They were divided into three groups, with 25 patients in each. Those in the first group received UKRAIN prior to their operation in the dosage of 5 mg every second day, to a total dosage of 50 mg, while those in the second group similarly received 10 mg of UKRAIN every second day to a total dosage of 100 mg. Those in the third (control) group were not treated with UKRAIN before their operation.

After treatment with UKRAIN, hardening of the tumor, and proliferation of connective tissues were observed. The ratio of T4/T8 lymphocytes increased by 30%. Eight to ten weeks after surgery, levels of ESR (a blood test to monitor inflammation in the body, which routinely increases after an operation) were found to be little more than half as high in the groups that had received UKRAIN, compared with the control group. This indicated faster post-operational healing and improvement in general condition of patients from the groups receiving UKRAIN.

The patients who were treated with a higher dosage of UKRAIN reported slight pain in the cancer area, and a slight increase in fever. However, faster tumour remission was observed in these patients.

The tumours appeared harder and slightly enlarged after UKRAIN therapy, and were easier to detect by ultrasound or radiological examination. Metastatic lymph nodes were also hardened and sclerotic (fibrous). Through this hardening process under the influence of UKRAIN, tumours and metastatic lymph nodes were clearly demarcated from healthy tissue and therefore easier to remove.

Complications such as prolonged lymphorrhoea (leakage of lymph), skin necrosis (death of skin tissue), suppuration of the wound, and pneumonia, all occurred in patients from the two UKRAIN groups at only half the rate than they appeared in patients from the control group.

Based on the results of this study the scientists from the Medical University Grodno recommended the use of UKRAIN, at the higher dosage, before all breast cancer operations.

## LUNG CANCER

In the tests of NCI Ukrain has been proven to be effective against both most important variants of lung cancer – non-small cell lung cancer and small lung cancer (slide). Its efficacy was later confirmed in a clinical study (Staniszewski et al, 1992) as well as in many clinical observations.

## MELANOMA

In several tests the effect of Ukrain on melanoma cell lines was evaluated. High uptake of Ukrain in melanoma cells *in vitro* was revealed in the study Hohenwarter et al, 1992.

Antimetastatic effect of Ukrain in mice with melanoma B-16 was studied. Ukrain was shown to inhibit the growth of the primary tumour and its metastases (Zemskov et al., 1996).

These results were confirmed in clinic. A long lasting benefit (12 years of no recurrence) was observed in a patient with a malignant nodular stage III melanoma, echo-reflexing zones in the ultrasound-scan of the liver and positive melanin excretion indicating diffuse metastasing at the time of diagnosis and who was subsequently treated with Ukrain (10 mg i.v., twice weekly) for 21 months (Hamler et al, 1996).

## BRAIN TUMORS

The effect of Ukrain on the expression of genes and proteins involved malignant growth in the cultured human glioblastoma cells (brain tumor) was investigated by the research group of Milano University, Italy.

Three human glioblastoma cell lines T60, T63 and GBM were treated with three concentrations of Ukrain (0.1, 1 and 10  $\mu\text{mol/l}$ ). Untreated cultures served as controls. The high dose (10  $\mu\text{mol/l}$ ) significantly reduced cell proliferation after 48 h and 72 h. There was also a tendency to downregulation of MMP-2 and SPARC 48 and 72 h after incubation with Ukrain. Ukrain influences some major aspects of progression in human glioblastoma cells, such as cell proliferation and the expression of a pivotal protein in the mechanisms, leading to tumor cell invasion and survival. Thus, Ukrain may have some potential for the therapy of brain tumors, and could well also help extend our understanding of the mechanisms of this anti-tumor and chemopreventive potential (Gagliano et al, 2006).

Successful use of Ukrain in the patients with brain tumors are illustrated in the following case reports.

In a 25 year old male patient a left sided, frontal chestnut-sized tumour was diagnosed and extirpated sub-totally. Histological examination demonstrated an anaplastic grade III astrocytoma. Treatment with Ukrain was started 7 weeks after the operation (cycles of 2x20 mg iv/w, for 5 weeks, with 2w treatment-free intervals between cycles). The tumour progression slowed down and the patient was still in good condition two years later (Steinacker et al, 1996).

In a 33 months- old female patient an astrocytoma of the optic nerve was diagnosed and extirpated sub-totally. The tumor progressed over the next 52 months. The patient received neither chemotherapy nor radiation. Treatment with Ukrain was started 52 months after the first operation (2 mg to 15 mg i.v., up to a total dose of 723 mg Ukrain over 13 months). Disease progression was slowed down and an almost stable condition was achieved (Steinacker et al, 1996a).

Another case of a 13-years old girl with a 2.2 cm large tumour in the region of the septum pellucidum, extending into interventricular foramina and obstructing the cerebrospinal fluid pathway. Following two previous interventions to evacuate the epidural hamartoma to drain the left ventricle due to hydrocephalus, the patient underwent partial tumour extraction. On histological examination a giant cell astrocytoma was found. Three months later treatment with Ukrain was started (2x5 mg i.v./week, 6 months) and remission was achieved. Tumour nodules seen in the CT diminished in size, three of five non-operated tumour nodules completely disappeared, as well as a CSF pathway obstruction and the neurological condition improved (Nowicky et al, 2003).

## OESOPHAGEAL CANCER

The efficacy of Ukrain in oesophageal cancer has been proven *in vitro* and then in a case report.

A patient with poorly differentiated squamous cell oesophageal carcinoma, inoperable according to clinical and X-ray contrast examinations, was treated first with 40 courses of radiation (maximal dose), followed by three courses of chemotherapy (cisplatin, methotrexate, bleomycin) without response. Nine months after the diagnose had been established, treatment with Ukrain was started (20 mg every 2<sup>nd</sup> day for 2 weeks, followed by 10 mg every 2<sup>nd</sup> day up to 230 mg). The patient was free of tumor recurrence up to the last observation 42 months later (Vyas et al, 1996).

It is well-known that often agents with promising preclinical results failed in clinical trials. This was not the case for UKRAIN where clinical use always confirmed good preclinical results. Moreover, Ukrain is effective also in cancer types where no *in vitro* study has been performed so far.

## BLADDER CANCER

28 patients with carcinoma of the bladder were divided into three groups for a prospective controlled clinical trial using either one, two or three cycles of UKRAIN therapy, with a two-week interval between cycles. Each cycle consisted of 10 mg/day intravenously, over 10 days. Tumors were assessed by cystoscopy and ultrasound before and two weeks after the end of treatment. Response to therapy (complete or partial remission) was observed in four from nine patients receiving one cycle of UKRAIN, in five from ten receiving two, and in eight from nine receiving three cycles. In no case was any growth of the tumour observed. No adverse events were reported. The authors concluded that better results are obtained with longer treatment. (Uglyanica et al, 1998).

## STOMACH CANCER

There are also case reports with successful treatment of stomach cancer with Ukrain.

## PROTECTION AGAINST RADIATION

Ukrain (0.4 mg/kg i.p) has been revealed to exert a protective effect on the endocrine system of irradiated rats. The numbers of thyroid hormone receptors and intracellular glucocorticoid receptors were normalized in NSC 631570-treated animals following short-term whole-body  $\gamma$ -irradiation (1 Gy) of rats (Luksa-Lichtenthaler et al, 2000a, b).

Animal studies showed that Ukrain conferred protection against the effects of irradiation. Mice subjected to a total body gamma irradiation corresponding to the LD<sub>70</sub> – LD<sub>90</sub>, showed a significantly higher survival rate (50-60% increase;  $p < 0.05$ ) when treated intraperitoneally with NSC 631570 at dose levels between 0.2 mg and 1.4 mg/kg. The highest survival rate was achieved when NSC 631570 was administered between 6 hours before and 3 hours after radiation. Several similar reports support the notion that NSC 631570 has radioprotective properties worthy of further investigation (Boyko et al, 1998a-d).

The effect of NSC 631570 as a radioprotective agent in normal human skin and lung fibroblasts was investigated using flow cytometry. Exponentially growing human cell lines were exposed to NSC 631570 (0.1-50  $\mu$ g/ml) for 1, 3 and 24 h or with additional exposure to radiation (1-10 Gy). Cells were also exposed to NSC 631570 (1.0  $\mu$ g/ml) for 24 h followed by radiation (2-8 Gy). Endpoints examined were: cytotoxicity, induction of apoptosis, cell cycle progression and TP53 and p21 protein expression. The following cell lines were used: MDA-MB-231 (human mammary tumour), PA-TU-8902 (pancreatic tumour), CCL-221 (colorectal tumour), U-138MG (glioblastoma), HSF1, HSF2, and CCD32-LU (all human lung fibroblast). NSC 631570 showed differential time- and dose-dependent inhibition of cell growth. The tumour cell lines exhibited greater sensitivity towards NSC 631570 than the normal skin and lung fibroblast lines. In combination, NSC 631570 and irradiation enhanced cytotoxicity for CCL-221 and U138MG cells but not for MDA-MB-231 or PA-TU-8902 cells. NSC 631570 was found to induce a radioprotective effect in normal human skin and lung fibroblasts. As determined by flow cytometry, NSC 631570 treatment resulted in an accumulation of CCL-221 and U-138MG in G<sub>2</sub>/M-phase. Its protective effect in normal human fibroblasts suggested that NSC 631570 could have beneficial properties while using in clinic combined with radio therapy (Cordes et al, 2002).

Physicians reported about beneficial effects of combined using Ukrain and radiation therapy: radiotherapy was better tolerated and side effects were alleviated.

## DRUG INTERACTIONS

*Analgesics (morphine)*

Conflicting evidence on the ability of UKRAIN to exert antinociception effects exist. In the writhing test in mice, 3% acetic acid was injected i.p. into mice previously treated with UKRAIN and 5 minutes later, the number of writhing episodes was noted. No therapeutic benefit was noted. However, in the hot plate test, UKRAIN given i.p. at 19 mg/kg, but not at 9.5 mg/kg, had a significant antinociceptive effect 15-60 minutes after administration. In addition, repeated i.p. administration of UKRAIN at doses of 2.375, 4.75, 9.5 and 19 mg/kg over 10 days was shown to be equivalent to 0.1 mg/kg morphine (Jagiello-Wojtowicz et al, 1996). UKRAIN has also been shown to interact with some analgesics: the analgesic action may be increased or impaired, depending on the pain model used. It was established that, during simultaneous treatment with morphine and UKRAIN over several days, the analgesic effects of morphine, as well as those of UKRAIN, were completely nullified (writhing test). Similarly, the antinociceptive effect of both single and repeated administration of UKRAIN was completely antagonised by naltrexone (Jagiello-Wojtowicz et al, 1998).

#### ***Anti-epileptics***

UKRAIN significantly ( $p < 0.001$ ) enhanced the anticonvulsive action of valproate in a mouse electroshock-induced seizure model. This was observed with UKRAIN doses of 9.5 and 19.0 mg/kg, but not at 4.75 mg/kg. No significant influence on the activity of other anti-epileptics (diazepam, carbamazepine, diphenylhydantoin, phenobarbital) was observed (Jagiello-Wojtowicz et al, 1992).

## CONCLUSION

To date UKRAIN has been tested on more than 100 cancer cell lines and has proved its malignotoxic effect against all of them, including pancreatic cancer cell lines and cell lines which were resistant to the chemotherapy drug cisplatin, as well human tumour xenografts. The wide spectrum of efficacy of Ukrain was confirmed in the following pilot study. 363 cancer patients with 47 different types of tumours were treated with UKRAIN between September 1997 and January 2003 at the Villa Medica Clinic (Edenkoben, Germany) under the medical direction of Dr. Aschhoff. These patients had already exhausted conventional means of therapy without success, and because of relapse and/or continued progression of the disease, UKRAIN therapy was undertaken. Nevertheless, the following rates of recovery (full remission) were achieved: breast cancer 31%, colorectal cancer 16.7%, lung adenocarcinoma 7.7%, small-cell lung carcinoma 21%, astrocytoma (brain tumor) 66.6%, neuroblastoma 60%, seminoma (testicular cancer) 75%, bladder carcinoma 50% (Aschhoff, 2003).

Toxicity studies, preclinical and clinical studies revealed Ukrain to be non-toxic and its use is safe. Because it triggers apoptosis in cancer cells Ukrain is only toxic against cancer cells while, in contrast to common chemotherapy, it leaves healthy cells undamaged. Through its antiangiogenic properties this medicine encapsulates tumours, thereby making them accessible to surgical intervention. In addition, Ukrain has an immune-modulating effect, whereby it improves the general condition of patients and does not only prolong their lives but in many cases also effects a recovery.

All this was the reason for physicians to use this medicine in the treatment of cancer patients also in many countries where an application for marketing authorisation for Ukrain has not been applied yet.

We allow us to publish here the references of physicians from these countries.

## ACKNOWLEDGMENT

All studies performed with UKRAIN so far were not financed by a pharmaceutical company but were investigator initiated studies. Researchers which performed these studies worked for the enrichment of world science and to enable better therapy of cancer patients. Having presented their research work on international congresses they awoke broad interest of the international scientific community.

They enabled broad clinical use of Ukrain and made a valuable contribution to the improving and saving many lives. We express our deep thanks to all these scientists. You may find their names among the authors in the following bibliography.

## BIBLIOGRAPHY

- (1) Nowicky JW. *New Immuno-stimulating anti-cancer preparation "Ukrain"*. 13<sup>th</sup> International Congress of Chemotherapy, Vienna, 28<sup>th</sup> August to 2<sup>nd</sup> September, 57, 1983, PS 12 5 33/A-6, part 288.
- (2) Nowicky JW. *Cancer Treatment Using Anticancer Preparation Alkaloid Derivative Ukrain*. IV Mediterranean Congress of Chemotherapy, 19-25 October 1984, Rhodos, Greece, Chemioterapia, Supplement to n. 2, Volume 4, 1169, April 1985.
- (3) Nowicky J, Greif M, Hamler F, Hiesmayr W, Staub W. *Biological Activity of Ukrain in Vitro and in Vivo*. V Mediterranean Congress of Chemotherapy. 26 October-1 November 1986 Cairo, Egypt, Chemioterapia, Supplement to n. 2, Volume 6, 683, June 1987.
- (4) Nowicky JW, Greif M, Hamler F, Hiesmayr W, Staub W. *Macroscopic UV-Marking through Affinity*. Journal of Tumor Marker Oncology, Volume 3, Number 4, 463, 1988.
- (5) Nowicky J, Hiesmayr W, Nowicky W. *Sensitisation for Specific Lysis in Target-Effektor-System with Derivatives of Chelidonium majus Alkaloids - Ukrain*. Extracted from the Proceedings of the 16<sup>th</sup> International Congress of Chemotherapy; 852. 1, June 1989, Israel.
- (6) Nowicky JW. *Biological and physiological effects of Ukrain*. Journal of Cancer Research and Clinical Oncology, Supplement Vol. 116, A3. 112. 46, 1990.
- (7) Slesak B, Nowicky JW, Harlozinska A. *In vitro effect of thiophosphoric acid derivatives from Chelidonium majus L. on normal lymphocyte subpopulations*. Journal of Cancer Research and Clinical Oncology, Supplement Vol. 116, A3. 112. 50, 1990.
- (8) Liepins A. *Enhancement of cell mediated lysis of tumor cells by Chelidonium majus L. Alkaloids (Ukrain)*. Journal of Cancer Research and Clinical Oncology, Supplement Vol. 116, A3. 118. 10, 1990.
- (9) Nowicky JW, Liepins A, Zbroja-Sontag W, Staniszewski A, Danilos J. Evaluation of clinical studies of Ukrain in cancer patients. Art:Bar.206, Zona:Barcel-fos, 29-Nov-90,09:37:310.
- (10) Nowicky JW, Staniszewski A, Zbroja-Sontag W, Slesak 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., XVII(2) 139, 1991.

- (11) Nowicky JW, Liepins A, Slesak B, Staniszewski A, Harlozinska-Szmyrka A, Zbroja-Sontag W, Danilos J. *Evaluation of clinical studies of Ukrain in cancer patients*. Journal of Chemotherapy, Supplement n. 4, 522, 1991.
- (12) Liepins A, Nowicky JW. *Ukrain is Selectively Cytostatic and/or Cytotoxic to Human Tumor and HIV-Infected Cells but not to Human Normal Cells*. Recent Advances in Chemotherapy, Anticancer Section, Proceedings of the 17<sup>th</sup> International Congress of Chemotherapy, Berlin, 2660, 1991.
- (13) Vatanasapt V, Wongpratoom W, Mairiang P, Mairiang E, Chaiyakam C, Buddhisawasd V, Pairojkul C, Nowicky JW. *Preliminary report on clinical experience in the use of Ukrain*. Thai Cancer Journal, Volume 17 No. 1-2, 20, 1991.
- (14) Nowicky JW, Liepins A, Staniszewski A, Slezak B, Nowicky W, Hiesmayr W. *The malignotoxic and immune modulating property of the alkaloid derivative Ukrain*. Journal of Cancer Research and Clinical Oncology, Suppl. Vol. 118, V1. 09. 05, 1992.
- (15) Kleinrok Z, Jagiello-Wojtowicz E, Matuszek B, Chodkowska A. *Basic Central Pharmacological Properties of Thiophosphoric acid alkaloid derivatives from Chelidonium Majus L.* Pol. J. Pharmacol. Pharm., Vol. 44, 227, 1992.
- (16) Remiszewska M, Wutkiewicz M, Jastrzebski Z, Czyzewska-Szafran H, Danysz A. *Pharmacological Effects of Ukrain in Rats and Rabbits*. Acta Poloniae Pharmaceutica-Drug Research, Vol. 49 no. 4, 43, 1992.
- (17) Liepins A, Nowicky JW. *Activation of Spleen Cell Lytic Activity by the Alkaloid Thiophosphoric Acid Derivative: Ukrain*. International Journal of Immunopharmacology, 14, 8, 1437-1442, 1992.
- (18) Slesak B, Nowicky JW, Harlozinska A. *In Vitro Effects of Chelidonium Majus L. Alkaloid Thiophosphoric Acid Conjugates (Ukrain) on the Phenotype of Normal Human Lymphocytes*. Drugs Exptl. Clin. Res., XVIII, 17, 1992.
- (19) Chlopkiewicz B, Marczevska J, Ejchart A, Anuszevska E, Koziorowska J. *Evaluation of Mutagenic; Genotoxic and Transforming Properties of Ukrain*. Drugs Exptl. Clin. Res., XVIII, 31, 1992.
- (20) Kleinrok Z, Jagiello-Wojtowicz E, Nowicky JW, Chodkowska A, Feldo M. *Interaction between Ukrain and Aminophenazone in Analgesic Test in Rodents*. Drugs Exptl. Clin. Res., XVIII, 97, 1992.
- (21) Musianowycz J, Judmajer F, Manfreda D, Spängler P, Albrecht H, Hoffmann J, Meijer D. *Clinical Studies of Ukrain in Terminal Cancer Patients (Phase II)*. Drugs Exptl. Clin. Res., XVIII, 45, 1992.
- (22) Danilos J, Zbroja-Sontag W, Baran E, Kurylcio L, Kondratowicz L, Jusiak L. *Preliminary studies on the effect of Ukrain (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] phenanthri-dinium-6-ol]-ethaneaminy} phosphinesulfide·6HCl) on the immunological response in patients with malignant tumours*. Drugs Exptl. Clin. Res., XVIII, 55, 1992.
- (23) Wyczolkowska J, Czuwaj M, Maslinski C. *The immunomodulating preparation Ukrain does not induce anaphylactic sensitization in mice and guinea pigs*. Drugs Exptl. Clin. Res., XVIII, 35, 1992.
- (24) Nowicky JW, Manolakis G, Meijer D, Vatanasapt V, Brzosko WJ. *Ukrain both as an anticancer and immunoregulatory agent*. Drugs Exptl. Clin. Res., XVIII, 51, 1992.
- (25) Staniszewski A, Slesak B, Kolodziej J, Harlozinska-Szmyrka A, Nowicky JW. *Lymphocyte subsets in patients with lung cancer treated with thiophosphoric acid alkaloid derivatives from Chelidonium majus L. (Ukrain)*. Drugs Exptl. Clin. Res., XVIII, 63, 1992.

- (26) Sotomayor E, Rao K, Lopez DM, Liepins A. *Enhancement of macrophage tumouricidal activity by the alkaloid derivative Ukrain. In vitro and in vivo studies.* Drugs Exptl. Clin. Res., XVIII, 5, 1992.
- (27) Pengsaa P, Wongpratoom W, Vatanasapt V, Udomthavornasuk B, Mairieng E, Tangvorapongchai V, Pesi M, Krusan S, Boonvisoot V, Nowicky JW. *The effects of thiophosphoric acid (Ukrain) on cervical cancer, stage IB bulky.* Drugs Exptl. Clin. Res., XVIII, 69, 1992.
- (28) Lohninger A, Hamler F. *Chelidonium majus L. (Ukrain) in the treatment of cancer patients.* Drugs Exptl. Clin. Res., XVIII, 73, 1992.
- (29) Kleinrok Z, Jagiello-Wojtowicz E, Nowicky JW, Chodkowska A, Feldo M, Matuszek B. *Some pharmacological properties of prolonged administration of Ukrain in rodents.* Drugs Exptl. Clin. Res., XVIII, 93, 1992.
- (30) Juskiewicz T, Minta M, Wlodarczyk B, Biernacki B. *Teratological evaluation of Ukrain in hamsters and rats.* Drugs Exptl. Clin. Res., XVIII, 23, 1992.
- (31) Jagiello-Wojtowicz E, Kleinrok Z, Surmaczynska B, Baran E, Feldo M, Nowicky JW. *Effect of single and three months treatment with Ukrain on amino-transferases (ALT and AST) and on the serum protein level in rodents.* Drugs Exptl. Clin. Res., XVIII, 85, 1992.
- (32) Jagiello-Wojtowicz E, Kleinrok Z, Nowicky JW, Matuszek B, Baran E, Surmaczynska B. *Effect of single and prolonged administration of Ukrain on prolactin concentration in rats.* Drugs Exptl. Clin. Res., XVIII, 89, 1992.
- (33) Jagiello-Wojtowicz E., Kleinrok Z., Matuszek B., Surmaczynska B., Baran E., Nowicky W., Nowicky J.W. *Effect of three months treatment with Ukrain on peripheral blood morphology in rodents.* Drugs Exptl. Clin. Res., XVIII, 79, 1992.
- (34) Jagiello-Wojtowicz E., Kleinrok Z., Feldo M., Chodkowska A., Nowicky J.W. *Effect of Ukrain on the efficacy of anti-epileptic drugs against maximal electroshock-induced seizures in mice.* Drugs Exptl. Clin. Res., XVIII, 107, 1992.
- (35) Jagiello-Wojtowicz E., Kleinrok Z., Chodkowska A., Feldo M., Nowicky J.W. *Modification of antinociceptive action of morphine by Ukrain in rodents.* Drugs Exptl. Clin. Res., XVIII, 101, 1992.
- (36) Hohenwarter O., Strutzenberger K., Katinger H., Liepins A., Nowicky J.W. *Selective inhibition of in vitro cell growth by the anti-tumour drug Ukrain.* Drugs Exptl. Clin. Res., XVIII, 1, 1992.
- (37) Danysz A., Kokoschinegg M., Hamler F. *Clinical studies of Ukrain in healthy volunteers (phase I).* Drugs Exptl. Clin. Res., XVIII, 39, 1992.
- (38) Brüller W. *Studies concerning the effect of Ukrain in vivo and in vitro.* Drugs Exptl. Clin. Res., XVIII, 13, 1992.
- (39) Nowicky J.W. *Biological Properties of Ukrain in Experimental and Clinical Investigations.* International Medical Reviews, Avalanche Ltd. St. Petersburg, Russia, 1, 1, 5, 1993.
- (40) Nowicky J.W., Nowicky W., Liepins A. *Cytostatic and cytotoxic effects of Ukrain on malignant cells.* VIII Mediterranean Congress of Chemotherapy, 24-29 May 1992, Athens, Greece, Journal of Chemotherapy, Supplement n. 1, Volume 5, 797, 1993.
- (41) Nowicky J.W. *Ukrain Antineoplastic Immunostimulant.* E09/029, NSC-631570, NSC-B238865, UKSR-222, W122, Drugs of the Future, Prous Science Publishers, Copyright Prous Science, 18 (11), 1015, November 1993.
- (42) Kamyshentsev M.V., Voltchek I.V., Btailovskaya I.V., Leschev A.L., Lavinsky Y.C. and Nowicky J. W. *Testing Ukrain as an Anti-Influenza Remedy.* Recent Advances in Chemotherapy, American Society for Microbiology, Proceedings of the 18th International Congress of Chemotherapy, Stockholm, Sweden, June 27-July 2, 645, 1993.

- (43) Liepins A., Sotomayor E. M., Lopez D. M. and J.W. Nowicky. *Biological Response-Modifying Properties of the Alkaloid Derivative Ukrain (NSC 631570)*. Recent Advances in Chemotherapy, American Society for Microbiology, Proceedings of the 18th International Congress of Chemotherapy, Stockholm, Sweden, June 27-July 2, 783, 1993.
- (44) Nowicky J. W., Manolakis G., Meijer D., Vatanasapt V., Brzosko W.J. and Lohninger A. *Immunological and Tumoricidal Properties of Ukrain*. Recent Advances in Chemotherapy, American Society for Microbiology, Proceedings of the 18th International Congress of Chemotherapy, Stockholm, Sweden, June 27-July 2, 793, 1993.
- (45) Lohninger A., Musianowyc J., Judmaier F., Manfreda D., Spängler P., Albrecht H., Hoffmann J. and Mejer D. *Results of Phase II Clinical Studies with Ukrain*. Recent Advances in Chemotherapy, American Society for Microbiology, Proceedings of the 18th International Congress of Chemotherapy, Stockholm, Sweden, June 27-July 2, 794, 1993.
- (46) Voltchek I.V., Nowicky J.W., Zolotukhin N.N., Kamyshtentsev M.V., Miroshnichenko A.G., Leschev A.L. and Belskikh A.N. *Some Immunohematological Effects of Ukrain*. Recent Advances in Chemotherapy, American Society for Microbiology, Proceedings of the 18th International Congress of Chemotherapy, Stockholm, Sweden, June 27-July 2, 798, 1993.
- (47) Nowicky Jaroslaw W., Markowska Janina and Brzosko Witold J. *Ukrain and Natural Killer Cells*. Recent Advances in Chemotherapy, American Society for Microbiology, Proceedings of the 18th International Congress of Chemotherapy, Stockholm, Sweden, June 27-July 2, 863, 1993.
- (48) Zemskov V.S., Yaremchuk O.Ya., Susak Ya.M., Deneka E.R., Kravchenko O.V. and Kamenets L.Ya. *Experience of the Application of Ukrain in Oncological Practice in Ukraine*. Recent Advances in Chemotherapy, American Society for Microbiology, Proceedings of the 18th International Congress of Chemotherapy, Stockholm, Sweden, June 27-July 2, 870, 1993.
- (49) Nowicky J.W., Cisak E., Liepins A., Susak Ja.M., Semskow W. *Stimulation of phagocytic activity in vitro, in vivo and in the clinic by Ukrain*. 11<sup>th</sup> Future Trends in Chemotherapy, Interdisciplinary World Congress on Antimicrobial and Anticancer Drugs, 24-27 April 1994, Palexpo Geneva (Switzerland), Abstracts: abs. 68, April 1994.
- (50) Kurik M.V., Susak Y.M., Kravchenko O.V. *Some biophysical properties of Ukrain*. 11<sup>th</sup> Future Trends in Chemotherapy, Interdisciplinary World Congress on Antimicrobial and Anticancer Drugs, 24-27 April 1994, Palexpo Geneva (Switzerland), Abstracts: abs. 79, April 1994.
- (51) Lisnyak O.I., Lozjuk R. M. *Biological activity of some thiophosphamide derivatives of alkaloids with respect to influenza virus*. 11<sup>th</sup> Future Trends in Chemotherapy, Interdisciplinary World Congress on Antimicrobial and Anticancer Drugs, 24-27 April 1994, Palexpo Geneva (Switzerland), Abstracts: abs. 96, April 1994.
- (52) Lozjuk R.M., Lisnyak O.I., Lozjuk L.V. *Theoretical grounds and experimental confirmation of antiviral effect of the preparation Ukrain*. 11<sup>th</sup> Future Trends in Chemotherapy, Interdisciplinary World Congress on Antimicrobial and Anticancer Drugs, 24-27 April 1994, Palexpo Geneva (Switzerland), Abstracts: abs. 95, April 1994.
- (53) Brzosko W.J., Graczyk A., Konarski J., Nowicky J.W. *Synergic influence of Ukrain and protoporphyrine amino conjugates on human malignant cell lines*. 11<sup>th</sup> Future Trends in Chemotherapy, Interdisciplinary World Congress on Antimicrobial and Anticancer Drugs, 24-27 April 1994, Palexpo Geneva (Switzerland), Abstracts: abs. 110, April 1994.

- (54) Brzosko W.J., Uglianica K., Fomin K., Nowicky J.W. Influence of Ukrain on breast cancers. 11<sup>th</sup> Future Trends in Chemotherapy, Interdisciplinary World Congress on Antimicrobial and Anticancer Drugs, 24-27 April 1994, Palexpo Geneva (Switzerland), Abstracts: abs. 109, April 1994.
- (55) Zemskov V.S., Susak Ya.M., Zemskov S.V. *Ukrain monotherapy for treatment of colorectal cancer*. 11<sup>th</sup> Future Trends in Chemotherapy, Interdisciplinary World Congress on Antimicrobial and Anticancer Drugs, 24-27 April 1994, Palexpo Geneva (Switzerland), Abstracts: abs. 78, April 1994.
- (56) Liepins A., Nowicky J.W. *Selective induction of programmed cell death (apoptosis) in malignant cells by the alkaloid derivative Ukrain (NSC-613570)*. 11<sup>th</sup> Future Trends in Chemotherapy, Interdisciplinary World Congress on Antimicrobial and Anticancer Drugs, 24-27 April 1994, Palexpo Geneva (Switzerland), Abstracts: abs. 93, April 1994.
- (57) Jagiello-Wojtowicz E., Kleinrok Z., Nowicky J., Hodkowska A., Feldo M., Matuszek B., Jablonska M., Gorzelak M. *Effect of six month treatment with Ukrain on early osteoporosis induced by ovariectomy in rats*. 11<sup>th</sup> Future Trends in Chemotherapy, Interdisciplinary World Congress on Antimicrobial and Anticancer Drugs, 24-27 April 1994, Palexpo Geneva (Switzerland), Abstracts: abs. 49, April 1994.
- (58) Nowicky J.W., Wladyslawa Nowicky, Hiesmayr W., Potopalsky A.. *Alterations of DNA; RNA and protein synthesis in malignant cells under the influence of Ukrain*. XVI International Cancer Congress 1994, 30 October - 5 November 1994, New Delhi, India, abs. PSB 15 -17, 319.
- (59) Voltchek I. *Ukrain - Drug of the Future in the Cancer Treatment?* Terra Medica, Nr. 1, 1995, 24 - 25 (in Russian).
- (60) Ciebiada I., Korczak E., Denys A., Nowicky J. W. *Effect of Ukrain preparation on immune response in mice affected by influenza virus*. Journal of Chemotherapy, Vol. 7 (Suppl.), n. 4, 1995 101-104.
- (61) Voltchek I., Kamyshtentsev M., Lavinsky Y., Nowicky J., Medvedev Y., Litvinchuk L. *Comparative Study of the Cytostatic Effects of Oliphen and Ukrain*. Journal of Chemotherapy, Vol. 8 - n. 2, 1996, 144-146.
- (62) 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., Vol. XXII (Suppl.), 1996, 1 - 7.
- (63) Nowicky JW, Hiesmayr W, Nowicky W, Liepins A. *Influence of Ukrain on DNA, RNA and Protein Synthesis in Malignant Cells*. Drugs Exptl. Clin. Res., XXII (Suppl.), 1996, 9-19.
- (64) Nowicky J.W., Hiesmayr W., *Influence of Ukrain on Human Xenografts in vitro*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 21 - 25.
- (65) Jin Y.M., Nowicky J.W., Liepins A. *Mitogenic Properties of Ukrain (NSC-631570) on Human Peripheral Blood Monocytes: Clinical Implications*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 27 - 30.
- (66) Liepins A., Nowicky J.W. *Modulation of Immune Effector Cell Cytolytic Activity and Tumour Growth Inhibition in vivo by Ukrain (NSC-631570)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 31 - 42.
- (67) Susak Y.M., Zemskov V.S., Yaremchuk O.Y., Kravchenko O.B., Yatsyk I.M., Korsh O.B. *Comparison of Chemotherapy and X-ray Therapy with Ukrain Monotherapy for Colorectal Cancer*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 43 - 50.
- (68) Uglianica K.N., Fomin K.A., Nefyodov L.I., Nowicky J.W., Brzosko W.J., Jankowski A. *Influence of Ukrain on Patients with Surgically Treated Breast Cancer (Introductory Remarks)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 51 - 54.

- (69) Uglanica K.N., Brzosko W.J, Fomin K.A., Nowicky J.W. *Influence of Ukrain on Breast Cancer*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 55 - 62.
- (70) Uglanica K.N., Fomin K.A., Nefyodov L.I., Nowicky J.W., Brzosko W.J., Jankowski A. *Influence of Ukrain on Patients with Surgically Treated Breast Cancer. Part I. Clinical and Laboratory Parameters*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 63 - 66.
- (71) Uglanica K.N., Fomin K.A., Nefyodov L.I., Vilkiewich T.W., Nowicky J.W., Brzosko W.J., Jankowski A. *Influence of Ukrain on Patients with Surgically Treated Breast Cancer. Part II. Hormonal Profile*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 67 - 70.
- (72) Uglanica K.N., Fomin K.A., Nefyodov L.I., Djurd T.I., Nowicky J.W., Brzosko W.J., Jankowski A. *Influence of Ukrain on Patients with Surgically Treated Breast Cancer. Part III. The Immune System*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 71 - 74.
- (73) Uglanica K.N., Maciuk J.R., Fomin K.A., Nefyodov L.I., Kravchuk R.I., Vinogradova L. M., Nowicky J.W., Brzosko W.J. *Influence of Ukrain on Patients with Surgically Treated Breast Cancer. Part IV. Electromicroscopic and Cytochemical Evaluation*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 75 - 82.
- (74) Nefyodov L.I., Uglanica K.N., Smirnov V.Y., Doroshenko Y.M., Fomin K.A., Nowicky J.W., Brzosko W.J. *Amino Acids and Their Derivatives in Blood Plasma of Patients with Breast Cancer Treated with Ukrain. Part V*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 83 - 86.
- (75) Nefyodov L.I., Uglanica K.N., Smirnov V.Y., Doroshenko Y.M., Fomin K.A., Nowicky J.W., Brzosko W.J. *Amino Acids and Their Derivatives in Tumour Tissue from Patients with Breast Cancer Treated with Ukrain. Part VI*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 87 - 90.
- (76) Nowicky J.W., Hiesmayr W., Liepins A. *Influence of Ukrain on Immunological Blood Parameters in vitro and in vivo*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 91 - 94.
- (77) Boyko V.N., Voltchek I.V., Petrov A.S., Bubnov V.P. *Action of Ukrain, a Cytostatic and Immunomodulating Drug, on Effects of Irradiation*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 95 - 100.
- (78) Jagiello-Wojtowicz E., Kleinrok Z., Nowicky J.W., Jablonski M., Gorzelak M., Chodkowska A., Feldo M., Matuszek B. *Effect of Six-Month Treatment with Ukrain on Early Osteoporosis Induced by Ovariectomy in Rats. Part I: Preliminary Studies of Bone Parameters*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 101- 104.
- (79) Jagiello-Wojtowicz E., Kleinrok Z., Nowicky J.W., Chodkowska A., Feldo M., Surmaczynska B., Gorzelak M., Jablonski M. *Effect of Six-Month Treatment with Ukrain on Early Osteoporosis Induced by Ovariectomy in Rats. Part II: Preliminary Studies of Peripheral Blood Parameters*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 105-108.
- (80) Jagiello-Wojtowicz E., Kleinrok Z., Nowicky J.W., Baran E. *Effect of Six-Month Treatment with Ukrain on Early Osteoporosis Induced by Ovariectomy in Rats. Part III: Preliminary Studies of Some Hormone Levels*. Drugs Exptl. Clin. Res., XXII (Suppl.), 1996, 109-113.
- (81) Susak Y.M., Kurik M.V., Kravchenko O.V., Zemskov S.V. *Certain Biophysical Properties of Ukrain*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 113 - 116.
- (82) Zhalilo LI, Susak YM, Zemskov SV, Susak IA. *Influence of Ukrain on the Redox Processes of Hepatocytes*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 117-120.
- (83) Brzosko W.J., Graczyk A., Konarski J., Nowicky J.W. *Synergic Influence of Ukrain and protoporphyrin Amino Acids Conjugates on Human Malignant Cell Lines*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 121 - 122.

- (84) Wyczółkowska J., Michon T., Nowicky J.W. *Inhibitory Effect of Thiophosphoric Acid Alkaloid Derivatives from Chelidonium majus L. (Ukrain) on Ovalbumin Antigenicity and Antiovalbumin IgE Antibody Response in Mice*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 123 - 128.
- (85) Jagiello-Wojtowicz E., Kleinrok Z., Chodkowska A., Nowicky J.W., Piper H., Kubiowski T. *Antinociceptive Effect of Ten Day Administration of Ukrain in Mice and Interaction of the Treatment with Morphine*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 129 - 132.
- (86) Jagiello-Wojtowicz E., Kleinrok Z., Nowicky J.W., Chodkowska A., Kubiowski T., Piper H. *Interaction Between Ukrain and Morphine in Their Ten-Day Treatment in Mice in the Writhing Syndrome Test*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 133 - 134.
- (87) Ciebiada I., Korczak E., Nowicky JW, Denys A. *Does the Ukrain Preparation Protect Mice Against Lethal Doses of Bacteria?* Drugs Exptl Clin Res, XXII (Suppl), 1996, 135-140.
- (88) Lozjuk R.M., Lisnyak O.I., Lozjuk L.V. *Theoretical Grounds and Experimental Confirmation of the Antiviral Effect of the Preparation Ukrain*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 141 - 146.
- (89) Ciebiada I., Korczak E., Nowicky J.W., Denys A. *Estimation of Direct Influence of Ukrain Preparation on Influenza Viruses and the Bacteria E. coli and S. aureus*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 147 - 152.
- (90) Lisnyak OI, Lozjuk RM. *Biological Activity of Some Thiophosphamide Derivatives of Alkaloids with Respect to Influenza Virus*. Drugs Exptl. Clin. Res., XXII (Suppl.), 1996, 153-156.
- (91) Stabuc B., Benedicic D. *Ukrain with Chemotherapy in Malignant Melanoma (Case Report)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 159-162.
- (92) Hamler F., Hiesmayr W., Korsh O.B., Melnyk A. *Ukrain Monotherapy in Malignant Melanoma (Case Report)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 163 - 166.
- (93) Kotsay B., Lisnyak O., Myndiuk O., Romanyshyn J., Fabri O. *Ukrain Treatment of Rhabdomyosarcoma (Case Report)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 167 - 170.
- (94) Kadan P., Korsh OB, Melnyk A. *Ukrain Therapy of Recurrent Breast Cancer with Lung Metastases (Case Report)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 171-174.
- (95) Nowicky J.W., Schramm E., Godysch Y. *Biophysical Effects of Ukrain Therapy in a Patient with Breast Cancer (Case Report)*. Drugs Exptl Clin Res., Vol XXII (Suppl), 1996, 175-182.
- (96) Kroiss T., Melnyk A., Korsh O.B. *Ukrain Treatment in Carcinoma of the Cervix (Case Report)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 183 - 186.
- (97) Lohninger A, Korsh OB, Melnyk A. *Combined Therapy with Ukrain and Chemotherapy in Ovarian Cancer (Case Report)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 187 - 190.
- (98) Sakalo V.S., Korsh O.B., Melnyk A. *Ukrain Treatment in a Patient with Non-Seminomatous Germ-Cell Tumour of Testis (Case Report)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 191 - 194.
- (99) Vyas J.J., Jain V.K. *Ukrain Treatment in Carcinoma of the Oesophagus (Case Report)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 195 - 198.
- (100) Kadan P., Korsh O.B., Hiesmayr W. *Ukrain in the Treatment of Urethral Recurrent Carcinoma (Case Report)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 199 - 202.

- (101) Steinacker J., Kroiss T., Korsh O.B., Melnyk A. *Ukrain Treatment in a Frontal Anaplastic Grade III Astrocytoma (Case Report)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 203-206.
- (102) Steinacker J., Korsh O.B., Melnyk A. *Ukrain Therapy of a Recurrent Astrocytoma of the Optic Nerve (Case Report)*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 207 - 210.
- (103) Voltchek I.V., Liepins A., Nowicky J.W., Brzosko W.J. *Potential Therapeutic Efficacy of Ukrain (NSC 631570) in AIDs Patients with Caposi's Sarcoma*. Drugs Exptl. Clin. Res., Vol. XXII (Suppl.), 1996, 211 - 214.
- (104) Thakur M.L., De Fulvio J., Tong. J., John E., McDevitt M.R. and Damjanov I. *Evaluation of biological response modifiers in the enhancement of tumor uptake of technetium-99m labeled macromolecules*. Journal of Immunological Methods, 152 (1992), 209 – 216.
- (105) Jagiello-Wojtowicz E., Kleinrok Z., Chodkowska A., Misztal G., Jagiello G. *Preliminary pharmacokinetic studies of Ukrain in rats*.
- (106) Zemskov V.S., Yaremchuk O.Y., Susak Y.M., Deneka E.R., Kravchenko O.V., Yatsyk I.M. *The first experience in the using of the Ukrain preparation in the treatment of oncological patients in Ukraine*. Likarska Sprava, 1-2, (1024), 1996, 158 – 161.
- (107) Zemskov S.V., Susak Y.M., Todor I.N., Khasanova L.T., Mosienko V.S. *Antimetastatic effect of Ukrain and its influence on the oxygen and energy metabolism of mice with melanoma B-16*. Experimental Oncology, Vol. 18 (1996), 4, 405 – 408.
- (108) Zemskov V.S., Yaremchuk O.Y., Susak Y.M., Kravchenko O.V., Yatsyk I.M., Voltchek I.V. *Ukrain – noviy effektivniy preparat dla lecheniya raka tolstoy i pryamoy kishki*. In: Actualniye Voprosy Oncologii, St. Petersburg, 1996, 175 – 177 (in Russian).
- (109) Nefyodov L.I., Uglanica K.N., Smirnov V.Y., Doroshenko Y.M., Fomin K.A., Nowicky J.W., Brzosko W.J. *Swobodnie aminokisloty i ich proizvodnie v plasme krvi i opuholevoy tkani bolnih rakom molochnoy zhelezi na fone lecheniya novym protivopuholevim preparatom Ukrain*. In: Actualniye Voprosy Oncologii, St. Petersburg, 1996, 212 – 214 (in Russian).
- (110) Uglanica K.N., Fomin K.A., Nefyodov L.I., Nowicky J.W., Brzosko W.J. *Electronnomicroscopicheskiy i morphohistohimicheskiy analis vosdeystvia Ukrain na opuholevuyu tkan molochnoy zhelezy*. In: Actualniye Voprosy Oncologii, St. Petersburg, 1996, 175 – 177 (in Russian).
- (111) Jagiello-Wojtowicz E., Kleinrok Z., Urbanska E.M. *Ukrain (NSC-631570) in experimental and clinical studies: A review*. Drugs Exptl. Clin. Res., XXIV (5/6), 1998, 213 - 219.
- (112) Bondar G.V., Borota A.V., Yakovets Y.I., Zolotukhin S.E. *Comparative evaluation of the complex treatment of rectal cancer patients (chemotherapy and X-ray therapy, Ukrain monotherapy)*. Drugs Exptl. Clin. Res., XXIV (5/6), 1998, 221-226.
- (113) Uglanitsa K.N., Nechiporenko N.A., Nefyodov L.I., Brzosko W.J. *Ukrain therapy of stage T1N0M0 bladder cancer patients*. Drugs Exptl. Clin. Res., XXIV (5/6), 1998, 227-230.
- (114) Uglanitsa K.N., Nefyodov L.I., Brzosko W. *Evaluation of the efficacy of Ukrain in the treatment of breast cancer: Clinical and laboratory studies*. Drugs Exptl. Clin. Res., XXIV (5/6), 1998, 231-239.
- (115) Aschhoff B. *Ukrain and hyperthermia treatment in a patient with Ewing's sarcoma (case report)*. Drugs Exptl. Clin. Res., XXIV (5/6), 1998, 241-242.
- (116) Aschhoff B. *Ukrain treatment in a patient with stage IV neuroblastoma. A case report*. Drugs Exptl. Clin. Res., XXIV (5/6), 1998, 243-245.

- (117) Todor I.N., Kazmin S.D., Susak Ya.M., Ztmskov S.V. The influence of glucose, succinate, pH of the medium and higher temperature on the cytotoxic activity of the preparation Ukrain. *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 247-252.
- (118) Korolenko T.A., Svechnikova I.G., Filjushina E.E, Kaledin V.I., Vakulin G.M., Usynin I.F., Tsyrendordjiev D.D. Macrophage stimulation and antitumor effect of Ukrain. *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 253-260.
- (119) Svechnikova I.G., Korolenko T.A., Stashko J.F., Kaledin V.I., Nikolin V.P., Nowicky J.W. *The influence of Ukrain on the growth of HA-1 tumor in mice: The role of cysteine proteinases as markers of tumor malignancy.* *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 261-269.
- (120) Korolenko T.A., Kaledin V.I., Svechnikova I.G., Li X.V., Stashko J.F., Ilnitskaya S.I., Nikolin V.P. *Study of the antitumor effect of ukrain: The role of macrophage secretion of  $\alpha$ -1-proteinase inhibitor.* *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 271-276.
- (121) Kulik G.I. *Comparative in vitro study of the effects of the new antitumor drug Ukrain and several cytostatic agents on the thiol groups in the tissue of Guerin carcinoma and its resistance to cisplatin variant.* *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 277-280.
- (122) Deneka E.R. *Morphometric and kinetic analysis of the growth of experimental sarcoma-45 in the presence of Ukrain.* *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 281-285.
- (123) Kulik GI, Deneka ER, Todor IN, Karmozina LG. Study of acute toxicity of Ukrain in rats after intravenous injection. *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 287-293.
- (124) Jagiello-Wojtowicz E., Kleinrok Z., Feldo M., Chodkowska A., Szponar J., Urbanska E.M. Six-week treatment with Ukrain in rabbits. Part 1: Morphological parameters. *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 295-299.
- (125) Jagiello-Wojtowicz E., Kleinrok Z., Feldo M., Chodkowska A., Szklarczyk V., Urbanska E.M. *Six-week treatment with Ukrain in rabbits. Part II: Serum levels of gonadal hormones.* *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 301-304.
- (126) Jagiello-Wojtowicz E., Kleinrok Z. Feldo M., Chodkowska A., Szklarczyk V., Urbanska E.M. Six-week treatment with Ukrain in rabbits. Part III: Serum levels of thyroid hormones. *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 305-308.
- (127) Jagiello-Wojtowicz E, Kleinrok Z, Chodkowska A, Misztal G., Jagiello G. *Preliminary pharmacokinetic studies of Ukrain in rats.* *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 309-311.
- (128) Gorzelak M., Jablonski M., Patyra M., Jagiello-Wojtowicz E. Effect of intermittent three month treatment with different doses of Ukrain on subregional femoral bone mineral density of sexually mature female rats. *Drugs Exptl Clin Res*, XXIV (5/6), 1998, 313-316.
- (129) Jablonski M., Gorzelak M., Patyra M., Jagiello-Wojtowicz E. Effect of intermittent three-month treatment with different doses of Ukrain on subregional bone mineral density of the femur of ovariectomized rats. *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 317-320.
- (130) Jagiello-Wojtowicz E, Kleinrok Z, Chodkowska A, Szkodziak A, Siembida E, Gustaw K, Urbanska E. *Modification of antinociceptive action of Ukrain by endogenous nitric oxide in the writhing syndrome test in mice.* *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 321-325.
- (131) Jagiello-Wojtowicz E., Kleinrok Z., Gustaw K. Interaction between Ukrain and Naltrexone in the writhing syndrome test in mice. *Drugs Exptl. Clin. Res.*, XXIV (5/6), 1998, 327-330.

- (132) Boyko V.N., Zholus R.B. *A comparative evaluation of the influence of the complex drug Ukrain and its components on the effects of radiation.* Drugs Exptl. Clin. Res., XXIV (5/6), 1998, 331-333.
- (133) Boyko V.N., Belskiy S.N. *The influence of the novel drug Ukrain on hemo-and immunopoiesis at the time of its maximum radioprotective effect.* Drugs Exptl. Clin. Res., XXIV (5/6), 1998, 335-337.
- (134) Boyko V.N., Levshina Ye.V. *A study of the influence of a novel drug Ukrain on in vivo effects of low-dose ionizing radiation.* Drugs Exptl. Clin. Res., XXIV (5/6), 1998, 339-341.
- (135) Boyko V.N., Zholus R.B., Legeza V.I. *A study of the influence of different types of radioprotectors on the survival of mice treated with ionizing radiation over a wide dose range.* Drugs Exptl. Clin. Res., XXIV (5/6), 1998, 343-347.
- (136) Koshelnick Y., Moskvina E., Binder B.R., Nowicky J.W. *Ukrain (NSC-631570) inhibits angiogenic differentiation of human endothelial cells in vitro.* 17<sup>th</sup> International Cancer Congress, Rio de Janeiro, August 24-28, 1998, Monduzzi Editore, 91-95.
- (137) Uglyanitsa K.N., Nefyodov L.I., Nowicky J.W., Brzosko W.J. *The effect of Ukrain on cancer of the urinary bladder.* 17<sup>th</sup> International Cancer Congress, Rio de Janeiro, August 24-28, 1998, Monduzzi Editore, 1065-1068.
- (138) Voltchek I., Sologub T., Gontcharova L., Pokrovskaya L., Belozyorova L., Lamanova E. *Choice of Ukrain and interferon-alpha doses for the cancer patients therapy.*
- (139) Panzer A, Seegers JC. *Ukrain, a semisynthetic alkaloid of Chelidonium majus, is selectively toxic to malignant cells by causing a methapase block which results in apoptosis.* Proceedings of the American Association for Cancer Research, vol. 39, March 1998, New Orleans, LA, USA.
- (140) Panzer A., Joubert AM, Bianchi PC, Seegers JC. *The antimetabolic effects of Ukrain™, a Chelidonium majus alkaloid derivative, are reversible in vitro.* Cancer Letters 150 (2000), 85-92.
- (141) Nowicky W., Koshelnick Y., Binder B.R. *Ukrain – ein nicht toxisches hochwirksames Anti-Krebs-Arzneimittel.* In: Ganzheitliche Krebstherapie. 5. Wiener Dialog über Ganzheitsmedizin, Facultas-Universitätsverlag, 2000, 205-208 (in German).
- (142) Aschhoff B. *Erfahrungsbericht über Behandlungen mit einem Alkaloidderivat aus Chelidonium majus (Ukrain).* In: Ganzheitliche Krebstherapie. 5. Wiener Dialog über Ganzheitsmedizin, Facultas-Universitätsverlag, 2000, 209-214 (in German).
- (143) Ramadani M., Gansauge S., Braumüller H., Schlosser S., Beger H.G., Gansauge F. *Selective induction of apoptosis in pancreatic cancer cell lines by NSC-631570.* In: Chirurgisches Forum 2000 für experimentelle und klinische Forschung. 117. Kongreß der Deutschen Gesellschaft für Chirurgie, Berlin, 02.05.-06.05.2000, 79-83 (in German).
- (144) Aschhoff B. *Kombinationstherapie mit dem Alkaloidderivat aus Chelidonium majus plus regionaler Tiefenhyperthermie.* medizin 2000 plus, 4/2000, 74-76 (in German).
- (145) Panzer A, Joubert AM, Eloff JN, Albrecht CF, Erasmus E, Seegers JC. *Chemical analyses of ukrain, a semi-synthetic chelidonium majus alkaloid derivative, fail to confirm its trimeric structure.* Cancer Lett. 2000 Nov 28;160(2):237-41.
- (146) Panzer A, Hamel E, Joubert AM, Bianchi PC, Seegers JC. *Ukrain™, a semisynthetic chelidonium majus alkaloid derivative, acts by inhibition of tubulin polymerization in normal and malignant cell lines.* Cancer Lett., 2000 Nov 28;160(2):149-57.
- (147) Roublevskaia IN, Plevoda BV, Ludlow JW, Haake AR. *Induced G2/M arrest and apoptosis in human epidermoid carcinoma cell lines by semisynthetic drug Ukrain.* Anticancer Res. 2000 Sep-Oct;20(5A):3163-7.

- (148) Kazmin SD, Todor IN. *The effect of antitumor drug Ukrain on malignant proliferating cells being at different stages of cell cycle*. Intl J Med Biol Environ 28(1), 57-64 (2000).
- (149) Roublevskaia I.N., Haake A.R., Ludlow J.W., Polevoda B.V. *Induced apoptosis in human prostate cancer cell line LNCaP by Ukrain*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 141-147.
- (150) Roublevskaia I.N., Haake A.R., Polevoda B.V. *BCL-2 overexpression protects human keratinocyte cells from Ukrain induced apoptosis but not from G2/M arrest* Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 149-155.
- (151) Hruby R. *Ukrain: Acute toxicity after intravenous, intramuscular and oral administration in rats*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 157-161.
- (152) Doroshenko Y.M., Hodysh Y.Y., Uglyanitsa K.N., Nefyodov L.I. *A method for determination of Ukrain in blood plasma for monitoring and pharmacokinetic study*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 163-170.
- (153) Doroshenko Y.M., Karavay A.V., Hodysh Y.Y., Uglyanitsa K.N., Nowicky W.M., Nefyodov L.I. *The dynamics of concentration of the main fluorescent component of Ukrain in the tissues and blood plasma of rats with W-256 tumor after a single intravenous injection*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 171-177.
- (154) Zemskov V.S., Procopchuk O.L., Susak Y.M., Zemskov S.V., Hodysh Y.Y., Zemskova M.V. *Ukrain (NSC 631570) in the treatment of pancreas cancer*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 179-190.
- (155) Uglyanitsa K.N., Nechiporenko N.A., Nefyodov L.I., Doroshenko Y.M., Brzosko W., Nowicky W. *Results of Ukrain monotherapy of prostate cancer*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 191-193.
- (156) Nefyodov L.I., Uglyanitsa K.N., Nechiporenko N.A., Smirnov V.Y., Brzosko W., Karavay N.L. *New biochemical mechanisms of the anticancer effect of Ukrain in the treatment of cancer of the urinary bladder*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 195-199.
- (157) Uglyanitsa K.N., Nefyodov L.I., Doroshenko Y.M., Brzosko W.J. *Comparison of the efficacy of different doses of Ukrain in the combined treatment of breast cancer*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 201-221.
- (158) Uglyanitsa K.N., Nefyodov L.I., Brzosko V. *Comparative evaluation of the efficiency of various Ukrain doses in the combined treatment of breast cancer Report 1 Clinical aspects of Ukrain application*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 223-230.
- (159) Nefyodov L.I., Uglyanitsa K.N., Smirnov V.Y., Karavay A.V., Brzosko W. *Comparative evaluation of blood plasma and tumor tissue amino acid pool in radiation or neoadjuvant preoperative therapies of breast cancer with the antitumor drug Ukrain*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 231-237.
- (160) Uglyanitsa K.N., Nefyodov L.I., Karayedova L.M., Nowicky J.W., Brzosko W. *Clinical aspects of cancer treatment and new biochemical mechanisms of the drug Ukrain*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 239-247.
- (161) Aschhoff B. *Retrospective study of Ukrain treatment in 203 patients with advanced-stage tumors*. Drugs Exptl. Clin. Res., XXVI(2000), 249-252.
- (162) Zemskov S.V., Prokopchuk O.L., Susak Y.M. *Ukrain treatment in a patient with breast carcinoma. Case report*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 253-254.
- (163) Prokopchuk O.L., Zemskov S.V., Susak Y.M. *Ukrain treatment of a patient with retroperitoneal synovial sarcoma. Case report*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 255-256.
- (164) Prokopchuk O.L., Zemskov S.V., Susak Y.M. *Ukrain treatment in a patient with metastatic renal cell carcinoma extending to the vena cava inferior. Case report*. Drugs Exptl. Clin. Res., XXVI (5/6), 2000, 257-259.

- (165) Voltchek I., Sologub T., Nowicky J.W., Grigoryeva T., Belozyorova L., Belopolskaya M., Semenyako N., Lamanova E. *Preliminary results of individual therapy of chronic hepatitis C by Ukrain and interferon- $\alpha$* . *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 261-266.
- (166) Votrin I.I., Voltchek I.V., Kurochkin S.N. Kolobkov S.L. *Effects of Ukrain on the activities of DNA-nicking enzymes*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 267-273.
- (167) Kurochkin S.N., Kolobkov S.L., Votrin I.I., Voltchek I.V. *Induction of apoptosis in cultured Chinese hamster ovary cells by Ukrain and its synergistic action with etoposide*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 275-278.
- (168) Korolenko T.A., Djanayeva S.J., Falameyeva O.V., Wevers R.A., Filjushina E.E., Buzueva I.I., Kaledin V.I., Sandula J., Nowicky J. *Chitotriosidase as a new marker of macrophage stimulation in a tumor model treated with cyclophosphamide and Ukrain*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 279-283.
- (169) Korolenko T.A., Poteryaeva O.N., Djanayeva S.J., Svechnikova I.G., Kaledin V.I., Timofeyeva O.A., Filipenko M.L., Nowicky J. *Cystatin C in LS lymphosarcoma and HA-1 hepatoma treated with Ukrain and cyclophosphamide and involvement of apoptosis*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 285-292.
- (170) Djanayeva S.J., Korolenko T.A., Svechnikova I.G., Falameyeva O.V., Korolenko E., Kaledin V.I., Nowicky J. *Influence of Ukrain and cyclophosphamide administration on HA-1 murine hepatoma and LS lymphoma on aspartic proteinase cathepsin D*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 293-299.
- (171) Poteryaeva O.N., Falameyeva O.V., Korolenko T.A., Kaledin V.I., Djanayeva S.J., Nowicky J.W., Sandula J. *Cysteine proteinase inhibitor level in tumor and normal tissues in control and cured mice*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 301-306.
- (172) Luksa-Lichtenthaler G.L., Ladutko E.I., Nowicky J.W. *Influence of Ukrain on the nuclear thyroid hormone receptors after short-term  $\gamma$ -irradiation*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 307-310.
- (173) Luksa-Lichtenthaler G.L., Ladutko E.I., Nowicky J.W. *Radiomodification effects of Ukrain, a cytostatic and immunomodulating drug, on intracellular glucocorticoid reception during short-term  $\gamma$ -irradiation*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 311-315.
- (174) Jablonski M. *Ukrain (NSC 631570) influences on bone status: A review*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 317-320.
- (175) Jablonski M., Gorzelak M., Patyra M., Jagiello-Wojtowicz E. *Intermittent three-month treatment with Ukrain in intact and ovariectomized rats. Part I: Effect on selected biomechanical parameters of the femur*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 321-325.
- (176) Jablonski M., Gorzelak M., Patyra M., Jagiello Wojtowicz E. *Intermittent three-month treatment with Ukrain in intact and ovariectomized rats. Part II: Effect on bone mineral density of the femur*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 327-331.
- (177) Jablonski M., Korczak W., Gorzelak M., Jagiello-Wojtowicz E. *Intermittent three-month treatment with Ukrain in intact and ovariectomized rats. Part III: Effect on the native electron paramagnetic resonance signal intensity of the femur*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 333-336.
- (178) Jagiello-Wojtowicz E., Dudka J., Dawidek-Pietryka K. *Effect of Ukrain on human liver alcohol dehydrogenase activity in vitro*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 337-339.
- (179) Uglyanitsa K.N., Nefyodov L.I., Doroshenko Y.M., Nowicky J.W., Volchek I.V., Brzosko W.J., Hodysh Y.J. *Ukrain: A novel antitumor drug*. *Drugs Exptl. Clin. Res.*, XXVI (5/6), 2000, 341-356.

- (180) Grinevich Yu.A., Bendyug G.D., Khranovska N.M., Martinenko S.V., Kadkalenko G.G., Novicky J.W. *Investigation of immunotropic activity of Ukrain in experiments*. Immunohiyya ta Alerholohiya, 1, 2001, 22-26 (in Ukrainian).
- (181) Gansauge F, Ramadani M, Gansauge S, Pressmar J, Muehling B, Strecker K, Cammerer G, Leder G, Beger HG. *Pancreatic Cancer and chemotherapy. New developments from bench to bedside. Progress in Pancreatology and GI-Tract Surgery*. Gastrointestinal Surgery Today – the Ulm Surgical School. September 2001.
- (182) Gansauge F, Ramadani M, Pressmar J, Gansauge S, Muehling B, Stecker B, Cammerer G, Leder G, Beger HG. *NSC-631570 (Ukrain) in the palliative treatment of pancreatic cancer. Results of a phase II trial*. Langenbeck's Archives of Surgery (2002), 386:570-574
- (183) Andrievski OM, Smalukh NV, Nowicky WM, Krivitski AK. *Vyvchennia vplyvu preparatu "Ukrain" na proyav actyvnosti trypsynopodobnyh proteasami in vitro*. Odeskyi Medychnyi Joornal, 1 (69), 2002:6-9
- (184) Cordes N, Plasswilm L, Bamber M, Rodemann HP. *Ukrain®, an alkaloid thiophosphoric acid derivative of Chelidonium majus L. protects human fibroblasts but not human tumour cells in vitro against ionizing radiation*. Int J Radiat Biol 2002, vol. 78, No. 1, 17-27.
- (185) Zemskov V, Prokopchuk O, Susak Y, Zemskov S, Tkachenko O, Hodysh Y, Nowicky W. *Efficacy of Ukrain in the treatment of pancreatic cancer*. Langenbeck's Archives of Surgery (2002) 387:84-89.
- (186) Gansauge F., Ramadani M., Beger H.G. *Ukrain beim fortgeschrittenen Pankreaskarzinom*. Ars Medici 2002, 22, 1056-1062.
- (187) Gansauge F. *Ukrain in Pancreatic cancer: Study Final Report*. University Ulm, 2002.
- (188) Aschhoff B. *Using UKRAIN in cancer patients: a clinical experience* (in print).
- (189) European Organization for Research and Treatment of Cancer. New Drug Development Office. *Ukrain (E90/029, W122, UKSR-222, NSC B238865): Screening results – human tumor xenografts in vitro*.
- (190) National Cancer Institute, National Institute of Health: Developmental Therapeutics Program. *NSC 631570: results of the Human Cell Line Screen*. Available at [www.dtp.nci.nih.gov](http://www.dtp.nci.nih.gov).
- (191) Aschhoff B. *Tumor-Arten*. [www.villamedica.de](http://www.villamedica.de).
- (192) Izdebska M, Jagiello Wojtowicz E. *Protective effects of thiophosphoric acid alkaloid from Chelidonium majus L. in rats intoxicated by methanol*. Pol J Eur, 2003, submitted.
- (193) Jagiello-Wojtowicz E, Maciejewska-Kozak H, Chodkowska A, Radej R. *The influence of chelidonine and Ukrain on the  $\beta$ 2-microglobulin concentration in the serum of lead-poisoned rats*. Herba Polonica, 2003, submitted.
- (194) Wielosz-Tokarzewska E, Jagiello-Wojtowicz E. *The effect of Ukrain on the serum VIP level in diabetic mice*. International Journal of Immunotherapy, XIX (2-4), 2003, 189-191.
- (195) Jagiello-Wojtowicz E, Kleinrok A, Jurek D. *Effects of Ukrain in acute intoxication with streptozotocin in rats*. International Journal of Immunotherapy, XIX (2-4), 2003, 193-196.
- (196) Jagiello-Wojtowicz E, Izdebska M, Piatkowska-Chmiel I. *The effect of Ukrain on selected biochemical parameters in the serum of methanol intoxicated rats*. International Journal of Immunotherapy, XIX (2-4), 2003, 197-200.
- (197) Yagodina OV, Nikolskaya EB, Faddejeva MD. *Inhibition of liver mitochondrial monoamine oxidase activity by alkaloids isolated from Chelidonium Majus and*

- Macleaya* and by derivative drugs "Ukrain" and "Sanguirythrine". *Tsitologiya*. 2003;45(10):1032-7. [Article in Russian].
- (198) Cordes N, Blaese MA, Plasswilm L, Rodemann HP, Van Beuningen D. *Fibronectin and laminin increase resistance to ionizing radiation and the cytotoxic drug Ukrain in human tumour and normal cells in vitro*. *Int J Radiat Biol*. 2003 Sep;79(9):709-720.
- (199) Poteriaeva ON, Korolenko TA, Svechnikova IG, Zhanaeva Sla, Falameeva OV, Kaledin VI, Nowicky W. [Cysteine proteinases and their inhibitors in the development of mouse HA-1 hepatoma and antineoplastic therapy]. *Biomed Khim* 2004 Mar-Apr;50(2):172-9. Russian.
- (200) Zhanaeva SY, Korolenko TA, Shilov AG, Halikova TA, Guthova IV, Margulis BA, Yarygina ES. *Effect of Ukrain on human lymphoma cell growth with different expressions of heat shock protein 70 (hsp70)*. *Int J Immunother* 2003, XIX(2-4): 33-39.
- (201) Aschhoff B. *Ukrain in the treatment of prostate cancer patients*. *Int J Immunother* 2003, XIX(2-4): 41-45.
- (202) Zahriychuk O. *Ukrain, a thiophosphoric acid derivative of alkaloids of *Chelidonium majus* L., is effective in the treatment of recurrent bronchopulmonary pathology in children from areas contaminated after the Chernobyl accident*. *Int J Immunother* 2003, XIX(2-4): 47-53.
- (203) Sologub TV, Voltchek IV, Kivisepp NA, Grigoryeva T. *Efficacy and safety of the drug Ukrain in chronic hepatitis C patients*. *Int J Immunother* 2003, XIX(2-4): 55-59.
- (204) Usova TA, Poteryaeva ON, Pospelova TI, Korolenko TA. *Serum cystatin C in patients with hemoblastosis*. *Int J Immunother* 2003, XIX(2-4): 61-65.
- (205) Gansauge F. *Treatment of pancreatic cancer patients with Ukrain: four case reports*. *Int J Immunother* 2003, XIX(2-4): 67-71.
- (206) Susak Y. *Ukrain stimulates fibrotic and sclerotic transformations of pancreatic cancer tissue: comparative description of six cases*. *Int J Immunother* 2003, XIX(2-4): 73-80.
- (207) Aschhoff B. *Retrospective study of Ukrain treatment in 28 patients with unresectable pancreatic cancer*. *Int J Immunother* 2003, XIX(2-4): 81-85.
- (208) Kleef R. *Ukrain (NSC 631570) in combination with locoregional hyperthermia in the treatment of pancreatic cancer with liver metastases: a case report*. *Int J Immunother* 2003, XIX(2-4): 87-90.
- (209) Kroiss T. *Ukrain in the therapy of advanced metastatic pancreatic cancer: a case report*. *Int J Immunother* 2003, XIX(2-4): 91-94.
- (210) Nowicki G, Zahriychuk O. *Ukrain treatment of astrocytomas in girl with tuberous sclerosis: a case report*. *Int J Immunother* 2003, XIX(2-4): 95-97.
- (211) Langer A, Zahriychuk O, Hodysh Y. *Treatment of generalized lymphangiomatosis with Ukrain: a case report*. *Int J Immunother* 2003, XIX(2-4): 99-103.
- (212) Aschhoff B. *Clinical improvement of a patient with xeroderma pigmentosum after treatment with Ukrain*. *Int J Immunother* 2003, XIX(2-4): a case report. *Int J Immunother* 2003, XIX(2-4): 105-108.
- (213) Nefyodov LI, Doroshenko YM, Smirnov VY, Uglyanitsa KN, Nowicky W. *Metabolic control and treatment of malignant growth: tumor development, patterns of amino acid imbalance and Ukrain*. *Int J Immunother* 2003, XIX(2-4): 109-114.
- (214) Melnichenko N, Sundikovich E, Makarchikov A, Zverinsky I. *Antioxidative status and lipid peroxidation in rats after administration of Ukrain*. *Int J Immunother* 2003, XIX(2-4): 115-119.
- (215) Zverinsky I, Maximchuk Y, Melnichenko N, Zaloga I. *Effect of Ukrain on hepatic drug-metabolizing enzymes in rats: pilot studies*. *Int J Immunother* 2003, XIX(2-4): 121-124.

- (216) Egorov A., Belanovskaya E, Rudyak T, Melnichenko N, Zverinsky I. *Assessment of the functional state and morphological structure of the liver of rats after administration of the drug Ukrain*. Int J Immunother 2003, XIX(2-4): 125-128.
- (217) Levina OA, Goncharova IA, Filatova TG, Nadeev AP, Nowicky W, Sukhenko TG, Kolesnikova OP, Korolenko TA. *Protective effect of Ukrain against acute acetaminophen-induced hepatitis in rats*. Int J Immunother 2003, XIX(2-4): 129-134.
- (218) Usova TA, Poteryaeva ON, Falameyeva OV, Zhanaeva SY, Levina OA, Yarygina ES, Korolenko TA, Nowicky W. *Serum cystatin C in murine tumors treated by combinations of cyclophosphamide with Ukrain or glucans*. Int J Immunother 2003, XIX(2-4): 135-140.
- (219) Zhanaeva SJ, Falameyeva OV, Filatova TG, Goncharova IA, Sukhenko TG, Kolesnikova OP, Kaledin VI, Korolenko TA, Nowicky WM. *Effect of different biological response modifiers on growth and metastazing of murine Lewis adenocarcinoma*. Int J Immunother 2003, XIX(2-4): 141-150.
- (220) Korolenko TA, Falameyeva OV, Poteryaeva OM, Zhanaeva SY, Levina OA, Nowicky W. *Cysteine protease inhibitor stefin A in murine tumors during treatment by Ukrain and/or cyclophosphamide*. Int J Immunother 2003, XIX(2-4): 151-157.
- (221) Todor I. *The effect of the antineoplastic drug Ukrain on the electrokinetic potential of malignant and normal cells*. Int J Immunother 2003, XIX(2-4): 159-167.
- (222) Andrievsky A, Smalyukh N, Krivitsky A, Zahriychuk O. *In vitro effects of Ukrain on the activity of trypsin-like proteases*. Int J Immunother 2003, XIX(2-4): 169-175.
- (223) Jablonski M. *Selected calciotropic hormones in serum of sexually mature female rats treated with Ukrain*. Int J Immunother 2003, XIX(2-4): 177-182.
- (224) Jablonski M. *Serum levels of corticosterone, progesterone, parathyroid hormone and calcitonin in ovariectomized rats after 3-month treatment with Ukrain*. Int J Immunother 2003, XIX(2-4): 183-188.
- (225) Wielosz-Tokarewska E, Jagiello-Wojtowicz E. *The effect of Ukrain on the serum vasoactive intestinal polypeptide level in diabetic mice*. Int J Immunother 2003, XIX(2-4): 189-191.
- (226) Jagiello-Wojtowicz E, Kleinrok A, Jurek D. *Effects of Ukrain in acute intoxication with streptozotocin in rats*. Int J Immunother 2003, XIX(2-4): 193-196.
- (227) Jagiello-Wojtowicz E, Izdebska M, Piatkowska-Chmiel I. *Effect of Ukrain on selected biochemical parameters in the serum of methanol-intoxicated rats*. Int J Immunother 2003, XIX(2-4): 197-200.
- (228) Jagiello-Wojtowicz E., Izdebska M.: *Effect of CNS-631570 (Ukrain) on selected biochemical parameters indicating liver dysfunction in acute methanol intoxication of rats*. Pol. J. Environ., 2004 w druku
- (229) Jagiello-Wojtowicz E., Piatkowska-Chmiel I.: *Effects of chelidonine on some biochemical parameters in the serum of rats subacutely intoxicated by copper*. Herba Polonica, 2004, Vol. 50, No ¼, 2004
- (230) Zemskov S.V. *Efficacy of adjuvant treatment with combination of Ukrain (NSC-631570) and Gemcitabin in cases of pancreas cancer*. Ukrainian Chemotherapeutic Journal 2005, #1-2
- (231) Mozhenok T.P., Belyaeva T.N., Leontieva E.A., Faddejewa M.D. *Modulation of vesicular membrane fusion and of actin cytoskeleton in mouse macrophages inducing by alkaloid sanguinarine and a derivative drug Ukrain*. Cytology 2005, #10. Institute of Cytology, RAS, St. Petersburg, Russia.
- (232) Tomaszewski M., Olchowik M. *Influence of Ukrain on some parameters in pelvis bone tissue of rats exposed to subacute microwave radiation*. Krajowe Sympozjum Studentkich Kół Naukowych Akademii Medycznej, Lublin, 15 stycznia 2005.

- (233) Olchowik M., Tomaszewski M. Effect of Ukrain on biochemical parameters of rats subjected to subacute microwave radiation (mW). Krajowe Sympozjum Studenckich Kół Naukowych Akademii Medycznych, Lublin, 15 stycznia 2005.
- (234) Piątkowska-Chmiel I. Porównanie działania chelidoniny i leku Ukrain w ostrych zatruciach miedzią i cyną u szczurów. Krajowe Sympozjum Studenckich Kół Naukowych Akademii Medycznych, Lublin, 15 stycznia 2005.
- (235) Izdebska M., Jagiełło-Wójtowicz E. Protective effects of NSC-631570 in rats acutely intoxicated by ethylene glycol. VII Sympozjum „Postępy Toksykologii Klinicznej i Sądowej”, Kraków, 2-4 czerwca 2005, *Przegl. Lek.*, 2005, t. 62, 6, s. 638.
- (236) Piątkowska-Chmiel I., Jagiełło-Wójtowicz E. Comparison of actions of Chelidonine and Ukrain in acute copper chloride intoxication in rats. VII Sympozjum „Postępy Toksykologii Klinicznej i Sądowej”, Kraków, 2-4 czerwca 2005, *Przegl. Lek.*, 2005, t. 62, 6, s. 638.
- (237) Izdebska M., Jagiełło-Wójtowicz E. Effect of single or 10-day treatment with Ukrain on some biochemical parameters in the serum of rats acutely intoxicated with alcohols. 42nd Congress of Toxicology, EUROTOX, Kraków, 11-14 September 2005, Vol. 158, Suppl. 1, s. 56-57.
- (238) Ernst E, Schmidt K: Ukrain – a new cancer cure? A systematic review of randomised clinical trials. *BMC Cancer*. 2005; 5: 69. doi: 10.1186/1471-2407-5-69.
- (239) Kleinrok A., Jagiełło-Wójtowicz E. Effects of Ukrain on some biochemical parameters In mice pretreated with streptozotocin. IV Lwowski-Lubelska Konferencja Biochemii Eksperymentalnej i Klinicznej, Lublin, 11-13 maja 2006.
- (240) Izdebska M., Jagiełło-Wójtowicz E. Effect of thiophosphoric acid alkaloid derivatives from *Chelidonium majus* L. on some biochemical parameters in the serum of rats acutely intoxicated by ethylene glycol. 5th International Symposium on Chromatography of Natural Products (ISCNP). The Application of Chromatographic Methods in Phytochemical & Biomedical analysis, Lublin -Kazimierz Dolny, June 19-22, 2006, P-58, s. 110.
- (241) Jagiełło-Wójtowicz E., Piątkowska-Chmiel I. Protective effects of chelidonine and Ukrain in rats acutely intoxicated with tin chloride. 5th International Symposium on Chromatography of Natural Products (ISCNP). The Application of Chromatographic Methods in Phytochemical & Biomedical analysis, Lublin -Kazimierz Dolny, June 19-22, 2006, P-60, s. 112.
- (242) Jagiełło-Wójtowicz E., Chodkowska A. Estimation of biochemical parameters in blood serum of rats subjected to 10-day treatment with alkaloid thiophosphoric acid derivative of *Chelidonium majus* L. (Ukrain) with simultaneous exposition to ionizing radiation. 5th International Symposium on Chromatography of Natural Products (ISCNP). The Application of Chromatographic Methods in Phytochemical & Biomedical analysis, Lublin -Kazimierz Dolny, June 19-22, 2006, P-61, s. 113.
- (243) Lanvers-Kaminsky C, Nolting DM, Köster J, Schröder A, Sandkötter J, Boos J (2006): In-vitro toxicity of Ukrain against human Ewing tumor cell lines. *Anticancer Drugs* 17(9): 1025-1030
- (244) Ernst E. Why there will never be an alternative cancer cure. *Anti-Cancer Drugs* 2006, 17: 1023-1024
- (245) Gagliano N, Moscheni C, Torri C, Magnani I, Bertelli AAE, Nowicky W and Gioia M (2006): Effect of Ukrain on matrix metalloproteinase-2 and Secreted Protein Acidic and Rich in Cysteine (SPARC) expression in human glioblastoma cells. *Anti-Cancer Drugs* 17:189-194.
- (246) Habermehl D, Kammerer B, Handrick R, Eldh T, Gruber C, Cordes N, Daniel PT, Plasswilm L, Bamberg M, Belka C, Jendrosseck V: Proapoptotic activity of Ukrain is based on *Chelidonium majus* L. alkaloids and mediated via a mitochondrial death pathway. *BMC Cancer* 2006; 6:14, <http://www.biomedcentral.com/1471-2407/6/14>.

- (247) Gansauge F, Ramadani M, Schwarz M, Beger HG, Lotspeich E, Poch B: The Clinical Efficacy of Adjuvant Systemic Chemotherapy with Gemcitabine and NSC-631570 in Advanced Pancreatic Cancer. *Hepato-Gastroenterology* 2007; 54:917-920
- (248) Jagiełło-Wójtowicz E., Izdebska M.: Effect of thiophosphoric acid alkaloids derivative from *Chelidonium majus* (L.) on antioxidant status in alcohol -intoxicated rats. *J. Ethnopharmacol.*, 2007 - submitted
- (249) Jagiełło-Wójtowicz E., Chodkowska A., Jabłoński M., Olchowik G.: Serum RANKL in rats treated with Ukrain and simultaneous exposition to ionizing radiation. *J. Ethnopharmacol.*, 2007 - submitted
- (250) Gagliano N, Moscheni C, Torri C, Donetti E, Magnani I, Costa F, Nowicky W and Gioia M (2007): Ukrain modulates glial fibrillary acidic protein, but not connexin 43 expression, and induces apoptosis in human cultured glioblastoma cells. *Anti-Cancer Drugs* 2007, 18: 669-676.
- (251) Check JB, Laniko AI: Effect of hypokinesia on cyclic nucleotides and hormonal regulation of calcium metabolism in rats. *East Afr Med J.* 2002 Apr; 79(4): 210-3
- (252) Rebscher H: Off-label use in oncology. Quackery or progress? *MMW Fortschr Med.* 2002 Oct 10; 144(41): 25-6. German.
- (253) Chibowski S, Zygmunt J: The influence of the sorptive properties of organic soils on the migration rate of <sup>137</sup>Cs. *J Environ Radioact.* 2002; 61 (2): 213-23.
- (254) Kuznetsova LP, Sochilina EE, Faddeeva MD, Iagodina OV: Effect of some isoquinoline alkaloids on enzymatic activity of acetylcholinesterase and monoamine oxidase. *Ukr Biokhim Zh.* 2005 Mar-Apr; 77(2): 147-53. Russian
- (255) Dudka J, Burdan F, Szumilo J, Tokarska E, Korobowicz A, Klepacz R, Gieroba R, Madej B, Korobowicz E: Effect of selected alcohol dehydrogenase inhibitors on human hepatic lactate dehydrogenase activity – an in vitro study. *J Appl Toxicol.* 2005 Nov-Dec; 25 (6): 549-53.
- (256) Grinevich Y, Shalimov S, Bendyuh G, Zahrychuk O, Hodysh Y: Effect of Ukrain on the growth and metastasizing of Lewis carcinoma in C57BL/6 mice. *Drugs Exp Clin Res.* 2005; 31(2): 59-70.
- (257) Mendoza J., Zamora R., Gallardo J., Ceballos G., Aldana A., Espinosa M., Maldonado V., Melendez-Zajgla: NF-kappaB Does Not Influence the Induction of Apoptosis by Ukrain. *Cancer Biology & Therapy* 5:7, July 2006: 788-793.