Research article

Ukrain – a new cancer cure? A systematic review of randomised clinical trials
E Ernst* and K Schmidt

Address: Complementary Medicine, Peninsula Medical School, Universities of Exeter & Plymouth, 25 Victoria Park Road, Exeter EX2 4NT

Email: E Ernst* - edzard.ernst@pms.ac.uk; K Schmidt - katja.schmidt@pms.ac.uk
* Corresponding author

Abstract

Background: Ukrain is an anticancer drug based on the extract of the plant Chelidonium majus L. Numerous pre-clinical and clinical investigations seem to suggest that Ukrain is pharmacologically active and clinically effective. We wanted therefore to critically evaluate the clinical trial data in the form of a systematic review.

Methods: Seven electronic databases were searched for all relevant randomised clinical trials. Data were extracted and validated by both authors, tabulated and summarised narratively. The methodological quality was assessed with the Jadad score.

Results: Seven trials met our inclusion criteria. Without exception, their findings suggest that Ukrain has curative effects on a range of cancers. However, the methodological quality of most studies was poor. In addition, the interpretation of several trials was impeded by other problems.

Conclusion: The data from randomised clinical trials suggest Ukrain to have potential as an anticancer drug. However, numerous caveats prevent a positive conclusion, and independent rigorous studies are urgently needed.

Background

Ukrain (NSC-631570) is a semi-synthetic compound derived from the common weed, greater celandine (Chelidonium majus L.). This plant contains a range of alkaloids, most notably chelidonine, also known as benzophenanthridine alkaloid. A leaflet distributed to patients at the Bristol Cancer Help Centre, United Kingdom, describes Ukrain as "the only known product, which at present does not also destroy healthy cells, and which reduces tumors and boosts the immune system..." [1]. Ukrain is most commonly administered intravenously and consists of one molecule thiophosphoric acid conjugated to three molecules of chelidonine. It has drug licenses in several states of the former Soviet Union.

Research on Ukrain started about 20 years ago. Meanwhile, numerous in-vitro studies [2-37] animal experiments [38-83], case reports [84-97], and case series [98-108] have emerged. Collectively, these data suggest that Ukrain has anticancer activity in a wide range of cell lines, which could be of clinical value. Whether or not this translates into clinical effectiveness and whether or not Ukrain does indeed cure some type of cancer or improves their prognosis can best be decided on the basis of randomised clinical trials (RCTs). This systematic review is aimed at summarising and critically evaluating all such studies.
Methods
Electronic literature searches were conducted in the following databases: MEDLINE (1966 to date, via Pubmed), EMBASE (1974 to date), CINAHL (Cumulative Index to Nursing and Allied Health Literature, 1982 to date), AMED (Allied and Complementary Medicine Database, 1985 to date), PsycINFO (1987 to date), DIMDI (Deutsches Institut für Medizinische Dokumentation und Information) and The Cochrane Central Register of Controlled Trials (CENTRAL). The following search terms were used: ‘Ukrain’, ‘chelidonium’, ‘greater celandine’, ‘cancer’, ‘neoplasm’ or ‘tumour’. Further handsearches were performed in our unit’s own files as well as in the reference lists of all located articles. The producer of Ukrain was also contacted. No restrictions regarding the language of publication were imposed.

We included all RCTs of Ukrain as a treatment for any type of human cancer. Ukrain could be used as a sole treatment or as an adjunct to conventional therapy. Any type of intervention was permitted in the control groups. The clinical endpoints had to be survival or parameters indicative of tumour burden. Non-randomised studies or RCTs that did not quantify clinical endpoints were excluded [e.g. [109-117]], as were duplicates [118].

All articles were read in full by both authors and data relating to design, diagnosis, number of subjects, treatments for experimental and control groups, outcome measures and results were extracted independently by both authors. The methodological quality of each trial was assessed using the Jadad score, unless the study was only available in abstract form [119]. It evaluates methodological quality using three items assessing random allocation, double-blinding and the reports of withdrawals and drop-outs and a maximum of 5 points can be given if all criteria are met. The authors agreed to a consensus on the assessed data and cases of discrepancy would be settled by discussion. Because of overt clinical heterogeneity, a meta-analysis was deemed unreasonable. Descriptive summaries of the data are presented in the following text.

Results
Our search strategy identified 7 RCTs [120-126]. The majority of these studies was published in two different journals between 1995 and 2002 by 4 different groups of authors from the Belarus and Germany. Key data from these studies are summarised in Table 1 and will be discussed below.

Susak et al published an RCT in which 108 colorectal cancer patients received either Ukrain as a monotherapy or 5-fluorouracil for an unspecified time duration [126]. The results suggest that this was followed by non-progression of the malignancy in 88.8% of the patients in the experimental group compared to 27.7% in the control group. This study is only reported in abstract form. Numerous methodological details are therefore not accessible and its methodological quality cannot be reliably assessed.

One year later, the same research group published a similar clinical trial, this time including 96 colorectal cancer patients [120]. Forty-eight patients received Ukrain as a monotherapy and 48 patients received 5-fluorouracil and radiation. The survival rate differed substantially between the two groups. Two-year survival was 78.6% in the experimental group compared to 33.3% in the control group. This study was not blinded but applied an appropriate method of randomisation.

Bondar et al treated 48 histologically verified rectal cancer patients either with X-ray radiotherapy, chemotherapy and surgery (control group) or with Ukrain and surgery (experimental group) [121]. Before and after these treatments, the authors measured 19 different laboratory parameters including two tumour markers. In addition, the Karnofsky Index, tumour dimensions, and recurrences were monitored. All of these variables strongly favoured Ukrain therapy over conventional treatment. This study has, however, numerous limitations. For instance, the method of randomisation was not explained; the authors merely stated that “all patients were subdivided into two randomised groups”. Moreover, “tumour dimensions” were mentioned as an outcome measure but neither the methodology of measurement nor the results were provided. The recurrence rates are expressed as percentage figures and no test statistics seem to have been applied.

Ugylanitsa et al conducted a study with 28 patients suffering from bladder cancer [116] aiming “to evaluate the efficacy of Ukrain”. Patients were allocated to three groups treated with a total dose of 100 (group 1), 200 (group 2), or 300 mg Ukrain (group 3). Two weeks later tumour regression was verified through cytoscopy and ultrasound. Complete and partial regression was noted in 0/4 patients of group 1, 1/4 patients of group 2, and 2/6 patients of group 3. This study lacks many characteristics of a rigorous trial; its stated aims (to evaluate efficacy) cannot be achieved with the study design, which essentially was that of an equivalence or dose-finding study.

Zemskov and colleagues published a “pilot study” with 42 patients suffering from pancreas cancer who had refused chemotherapy [122]. They were randomised to receive either Vitamin C alone or with Ukrain (total dose 100 mg/patient). The primary endpoint (survival) strongly favoured the Ukrain group. The analysis seems to include 4 protocol violations (the description is unclear). Even though the randomisation procedure is mentioned (‘closed envelopes’) it seems unusual that precisely 21
patients ended up in both groups. The results are surprisingly good – much better than with any other treatment for that condition.

Uglyanitsa et al randomised ("by lottery") 75 breast cancer patients into three groups of 25 patients each [123]. They received either no specific treatment, a total dose of 50 or 100 mg Ukrain 5–7 days before mastectomy. The authors note that Ukrain rendered the primary tumour and the affected regional lymph nodes smaller, harder and "more clearly defined". They interpret this as Ukrain-induced tumour sclerosis. According to the investigators' judgement, these changes facilitated surgery and the operative success. In addition, Ukrain was associated with remarkable symptomatic improvements, e.g. better appetite, more sleep, less weakness. The report is unclear in several respects. For instance, no details about statistical analyses are provided, the outcome measures seem subjective, no information regarding investigator blinding is given, and the randomisation procedure seems suspect.

Zemskov and colleagues randomised 42 patients with pancreatic cancer who had refused conventional therapy [124]. They received either Ukrain (total dose 100 mg/patient) with Vitamin C or Vitamin C alone. The results confirmed this group's earlier findings [122]. Survival was remarkable in the Ukrain treated patients and symptoms responded well to this treatment. There are, however, numerous puzzling details. Why do the authors call their second study a "pilot study"? Why did their ethics committee consent to this "placebo"-controlled trial in the knowledge of the surprisingly positive earlier results? How could a proper randomisation again result in two equally sized groups of 21? In the discussion, the authors describe their earlier results as though this trial was conducted against 5-FU which, in fact, is not the case [122].

Gansauge et al reported a study of 90 patients with pancreatic cancer treated either with 1000 mg gemcitabine/m² or 100 mg Ukrain or the combination of both regimens [125]. Survival rates suggested that Ukrain was superior to gemcitabine alone. A direct comparison of the 12 month survival rates revealed large differences compared to the data from Zemskov et al [124] (29% vs 76% in the Ukrain-treated groups). The randomisation procedure was not explained and, again, the equal group sizes are remarkable.

Conclusion
Collectively, these RCTs seem to suggest that Ukrain is an effective therapy for a range of cancers. In conjunction with the numerous encouraging case reports [84-97] case series [98-108], and non-randomised clinical trials [109-121] these data look impressive at first glance. Yet several important caveats need to be considered.

None of the RCTs in this systematic review is without serious methodological limitations. The Jadad score [119] of most RCTs was low. Their sample size was usually small, and a sample size calculation to define the number of patients required was lacking in most cases. Even though most RCTs were non-inferiority studies by design and purpose, their statistical approach was that of a superiority trial. The majority of RCTs were conducted in Ukrainian research institutes and published in only two different journals. In several trials, there are clear signs of involvement of the manufacturer of Ukrain. Most RCTs have generally been poorly evaluated and reported, which possibly reflects the poverty of clinical science in Eastern Europe. Independent replications are not available. The only German study [125] has also been heavily criticised: its sample size (30 patients in each group) is minute, the report lacks statistical detail and there is an inequality of treatment cycles between groups [127]. It was also noted that this study (the only RCT not published in the same two journals as all the other RCTs) was published in a journal for which the senior author served as editor [127]. No RCTs were found showing negative or near neutral results; this might suggest the existence of publication bias for which we did, however, find no definite proof.

Greater celandine (Chelidonium majus L.), which forms the basis of Ukrain, was traditionally used for liver and gallbladder complaints, loss of appetite and gastroenteritis. None of these indications is supported by trial evidence. The main alkaloid from this plant, chelidonine, has antispasmodic, weak central analgesic and papaverine-like effects. In animal experiments, an alcoholic extract of greater celandine increased bile flow, caused non-specific immune stimulation and acted as a hepatoprotectant [128]. The oral administration of greater celandine in humans has been associated with several cases of toxic hepatitis [129].

The mechanism of action of Ukrain as an antitumor drug (if any) remains elusive. Collectively, the preclinical studies are suggestive of antineoplastic and immunomodulatory effects. It has been postulated that the antineoplastic effect is due to the alkaloids interfering with the metabolism of cancer cells, diminished synthesis of DNA, RNA and proteins, the inhibition of cellular oxygen consumption, and the induction of programmed cell death in malignant cells [130].

Several reports of adverse reactions after greater celandine have been published. Most notably, toxic hepatitis has been associated with its oral use [129,131,132]. No case reports of adverse events have emerged of intravenous Ukrain therapy for cancer. The clinical trial data suggest that Ukrain might cause the following adverse effects: an increase in patients' body temperature (n = 26).
References

1. Miller S. Ukrain. Bristol Cancer Help Centre ‘handout’ dated 05/03/2004. (unpublished).
2. Nowicky J, Greif M, Hamler F, Hiesmayr W, Staub W: Biological activity of Ukrain in vitro and in vivo. Chemioterapia 1987, 6:683-5.
3. Hohenwarter O, Strutzbenberger K, Katzing H, Liepins A, Nowicky JW: Selective inhibition of in vitro cell growth by the antitumour drug Ukrain. Drugs Exp Clin Res 1992, 18:1-4.
4. Bruller W: Studies concerning the effect of Ukrain in vivo and in vitro. Drugs Exp Clin Res 1992, 18:13-6.
5. Slesak B, Nowicky JW, Harlozinska A: In vitro effects of Chelidonium majus L. alkaloid thio phosphoric acid conjugates (Ukrain) on the phenotype of normal human lymphocytes. Drugs Exp Clin Res 1992, 18:7-21.
6. Chlópiakiewicz B, Marczewska E, Jehlart A, Anuszewska E, Koziorowska J: Evaluation of mutagenic, genotoxic and transformatory properties of Ukrain. Drugs Exp Clin Res 1992, 18:31-4.
7. Sotomayor EM, Rao K, Lopez DM, Liepins A: Enhancement of macrophage tumouricidal activity by the alkaldol derivative Ukrain. In vitro and in vivo studies. Drugs Exp Clin Res 1992, 18:5-11.
8. Staniszewski A, Slesak B, Kolodziej J, Harlozinska-Szymkra A, Nowicky JW: Lymphocyte subsets in patients with lung cancer treated with thio phosphoric acid alkaldol derivatives from Chelidonium majus L. (Ukrain). Drugs Exp Clin Res 1992, 18:63-7.
9. Kleinrok Z, Jagiello-Wojtowicz E, Matuszek B, Chodkowska A Basic central pharmacological properties of thio phosphoric acid alkaldol derivatives from Chelidonium majus L. Pol Pharm 1992, 44:237-39.
10. Thakur ML, DelFuvio J, Tong J, John E, McDevitt MR, Damjanov I: Evaluation of biological response modifiers in the enhancement of tumor uptake of technetium-99 m labeled macro-molecules. A preliminary report. J Immunol Methods 1992, 152:209-16.
11. Liepins A, Nowicky JW: Activation of spleen cell lytic activity by the alkaldol thio phosphoric acid derivative: Ukrain. Int J Immunopharmacol 1992, 14:1137-42.
12. JodloWSka-Jedrych B: Morphological studies on rat's liver after a ten-day treatment with Chelidonium majus L. alkaldol thio phosphoric acid derivative (Ukrain). Ann Univ Mariae Curie Skłodowska (Med) 1994, 49:19-24.
13. Liepins A, Nowicky JW, Bustamente JO, Lam E: Induction of bimodal programmed cell death in malignant cells by the derivative Ukrain (NSC-631570). Drugs Exp Clin Res 1996, 22:73-9.
14. Nowicky JW, Hiesmayr W, Nowicky W, Liepins A: Influence of Ukrain on DNA, RNA and protein synthesis in malignant cells. Drugs Exp Clin Res 1996, 22:81-91.
15. Nowicky JW, Hiesmayr W, Nowicky W, Liepins A: Influence of Ukrain on human xenografts in vitro. Drugs Exp Clin Res 1996, 22:93-7.
16. Jin J, Nowicky JW, Liepins A: Mitogenic properties of Ukrain (NSC-631570) on human peripheral blood monocytes: clinical implications. Drugs Exp Clin Res 1996, 22:99-101.
17. Liepins A, Nowicky JW: Modulation of immune effector cell cyclic activity and tumour growth inhibition in vivo by Ukrain (NSC 631570). Drugs Exp Clin Res 1996, 22:103-13.
18. Susak YM, Kurik MV, Kravchenko OV, Zemskov SV: Certain biophysical properties of Ukrain. Drugs Exp Clin Res 1996, 22:185-7.
19. ZhaliLO Li, Susak YM, Zemskov SV, Susak JA: Influence of Ukrain on the redox processes of hepatocytes. Drugs Exp Clin Res 1996, 22:189-91.
20. Brzowski W, Graczyk A, Konarski J, Nowicky JW: Synergic influence of Ukrain and photophorpy amino acid conjugates on human malignant cell lines. Drugs Exp Clin Res 1996, 22:193-4.
21. Chlópiakiewicz B, Korczak E, Nowicky JW, Denyes A: Estimation of direct influence of Ukrain preparation on influenza viruses and the bacteria E. coli and S. aureus. Drugs Exp Clin Res 1996, 22:19-23.
22. Volzhek I, Kamshentsev M, Lavinsky Y, Nowicky JW, Medvedev Y, Litvinchuk L: Comparative study of the cytostatic effects of Oliphen and Ukrain. J Chemother 1996, 8:1-46.
23. Kornolenko TA, Kaledin VI, Svehckova IG, Li XV, Stashko JF, Ilinskaya SI et al: Study of the antitumour effect of Ukrain: the role of macrophage secretion of alpha-1-proteinase inhibitor. Drugs Exp Clin Res 1998, 24:271-6.
24. Kulkil GI: Comparative in vitro study of the effects of the new antitumour drug Ukrain and several cytostatic agents on the thiol groups in the tissue of Guerin carcinoma and its resistance to cisplatin variant. Drugs Exp Clin Res 1998, 24:277-80.
25. Boyko VN, Belskiy SN: The influence of the novel drug Ukrain on hemo- and immunopoiesis at the time of its maximum radioprotective effect. Drugs Exp Clin Res 1998, 24:335-7.
26. Panzer A, Joubert AM, Bianchi PC, Seegers JC: Ukrain™ a semisynthetic Chelidonium majus alkaldol derivative, acts by inhibition of tubulin polymerization in normal and malignant cell lines. Cancer Lett 2000, 160:149-57.
27. Panzer A, Joubert AM, Bloff JN, Albrecht CF, Erasmus E, Seegers JC: Chemical analyses of Ukrain, a semi-synthetic Chelidonium majus alkaldol derivative, fail to confirm its trimeric structure. Cancer Lett 2000, 160:237-41.
28. Roublevskaia IN, Polevoda BV, Ludlow JW, Haake AR: Induced G2/M arrest and apoptosis in human epidermoid carcinoma cell lines by semisynthetic drug Ukrain. Anticancer Res 2000, 20:3163-7.
29. Panzer A, Joubert AM, Bianchi PC, Seegers JC: The antimitotic effects of Ukrain, a Chelidominus majus alkaldol derivative, are reversible in vitro. Cancer Lett 2000, 150:85-92.
30. Panzer A, Joubert AM, Bianchi PC, Hamel E, Seegers JC: The effects of chelidomin on tubulin polymerisation, cell cycle progression and selected signal transmission pathways. Eur J Cell Biol 2001, 80:111-8.
31. Roublevskaia IN, Haake AR, Ludlow JW, Polevoda BV: Induced apoptosis in human prostate cancer cell line LNCaP by Ukrain. Drugs Exp Clin Res 2000, 26:141-7.
32. Roublevskaia IN, Haake AR, Polevoda BV: Bcl-2 overexpression protects human keratinocyte cells from Ukrain-induced apoptosis but not from G2/M arrest. Drugs Exp Clin Res 2000, 26:149-56.
33. Volzhek I, Sologub T, Nowicky JW, Grigoryeva T, Belozorovya L, Belopolskaya M, et al: Preliminary results of individual therapy of chronic hepatitis C by Ukrain and interferon-alpha. Drugs Exp Clin Res 2000, 26:261-6.
34. Votrin II, Votlchek IV, Kurochkin SN, Kolobkov SN: Effects of Ukrain on the activities of DNA-nicking enzymes. Drugs Exp Clin Res 1992, 18:267-73.

35. Jagiello-Wojtowicz E, Dudka J, Dawidek-Pietryka K: Effect of Ukrain on human liver alcohol dehydrogenase activity in vitro. Drugs Exp Clin Res 2000, 26:337-9.

36. Kuzneceva LP, Nikol'skaia EB, Sochilina EE, Paddeeva MD: The inhibition of the static hydrolysis of acetylcholine by acetylcholinesterase using principle alkaloids isolated from celandine and macleaya and their derivatives. Tislotologia 2001, 43:1046-50.

37. Cordes N, Blase MA, Plasswill L, Rodemann HP, Van Beuningen D: Fipron virus. J Chemother 1995, 7:101-4.

38. Kleinrock Z, Jagiello-Wojtowicz E, Nowicky JW, Chodkowska A, Feldo M, Matuszek B, Nowicky JW, Denys A: Some pharmacological properties of prolonged administration of Ukrain on rodents. Drugs Exp Clin Res 1992, 18:93-6.

39. Jagiello-Wojtowicz E, Kleinrock Z, Chodkowska A, Feldo M, Nowicky JW, Denys A: Modulation of anticoagulant activity of phospholipids by Ukrain in rodents. Drugs Exp Clin Res 1992, 18:101-5.

40. Jagiello-Wojtowicz E, Kleinrock Z, Feldo M, Chodkowska A, Nowicky JW: Effect of Ukrain on the efficacy of anti-epileptic drugs against maximal electroshock-induced seizures in mice. Drugs Exp Clin Res 1992, 18:107-9.

41. Juszkiewicz T, Minta M, Wiadarczyk B, Biernacki B: Teratological evaluation of Ukrain in hamsters and rats. Drugs Exp Clin Res 1992, 18:23-9.

42. Wyczolkowska J, Czszwaj M, Maslinski C: The immunomodulating preparation Ukrain does not induce anaphylactic sensitization in mice and guinea pigs. Drugs Exp Clin Res 1992, 18:35-8.

43. Jagiello-Wojtowicz E, Kleinrock Z, Matuszek B, Sumarczyznska B, Baran E, Nowicky W, et al.: Effect of three months treatment with Ukrain on peripheral blood morphology in rodents. Drugs Exp Clin Res 1992, 18:79-83.

44. Jagiello-Wojtowicz E, Kleinrock Z, Smarczyznska B, Baran E, Feldo M, Nowicky JW: Effect of single and three months treatment with Ukrain on aminotransferases (ALT and AST) and on the serum protein level in rodents. Drugs Exp Clin Res 1992, 18:85-7.

45. Jagiello-Wojtowicz E, Kleinrock Z, Nowicky JW, Matuszek B, Baran E, Smarczyznska B: Effect of single and prolonged administration of Ukrain on prolactin concentration in rats. Drugs Exp Clin Res 1992, 18:89-91.

46. Matuszek M, Krolowiska-Prasal I, Jedyrcy B: Histological appreciation of the stomach after the application of thiophosphoric acid derivatives of Chelidonium majus L. (Ukrain) alkaloids. Ann Univ Maris Carie Skodowska 1992, 47:123-6.

47. Ciebiada I, Korczak E, Denys A, Nowicky JW: Interaction between Ukrain and morphine in their ten-day treatment in mice in the writhing syndrome test. Drugs Exp Clin Res 1996, 22:205-6.

48. Ciebiada I, Korczak E, Nowicky JW, Denys A: Does the Ukrain preparation protect mice against lethal doses of bacteria? Drugs Exp Clin Res 1996, 22:207-11.

49. Lozjuk RM, Lisyynik OL, Lozjuk LV: Theoretical grounds and experimental confirmation of the antiviral effect of the preparation Ukrain. Drugs Exp Clin Res 1996, 22:213-7.

50. Lisyynik OL, Lozjuk RM: Biological activity of some thiophosphoric derivatives of alkaloids with respect to influenza virus. Drugs Exp Clin Res 1996, 22:225-8.

51. Todor IN, Kuzmin SD, Susak YaM, Zemskov SV: The influence of glucose, succinate, pH of the medium and higher temperature on the cytotoxic activity of the preparation Ukrain. Drugs Exp Clin Res 1998, 24:247-52.

52. Korolenko TA, Svechnikova IG, Filushina EA, Kaledin VI, Vakulin GM, Usyinin IF, et al.: Macrophage stimulation and antitumour effect of Ukrain. Drugs Exp Clin Res 1998, 24:233-60.

53. Svechnikova IG, Korolenko TA, Shtshoko JUF, Kaledin VI, Nikolpin VP, Nowicky JW: The influence of Ukrain on the growth of HA-1 tumor in mice: the role of cytostatic proteins as markers of tumor malignancy. Drugs Exp Clin Res 1998, 24:261-9.

54. Deneka ER: Morphometric and kinetic analysis of the growth of experimental sarcoma S-45 in the presence of Ukrain. Drugs Exp Clin Res 1998, 24:281-5.

55. Kulik GI, Deneka ER, Todor IN, Karmelozina LG: Study of acute toxicity of Ukrain in rats after intravenous injection. Drugs Exp Clin Res 1998, 24:287-93.

56. Jagiello-Wojtowicz E, Kleinrock Z, Matuszek B, Feldo M, Chodkowska A, Szponar J, Urbanska EM: Six-week treatment with Ukrain in rabbits. Part I: Morphological parameters. Drugs Exp Clin Res 1998, 24:295-9.

57. Jagiello-Wojtowicz E, Kleinrock Z, Feldo M, Chodkowska A, Szklarczyk V, Urbanska EM: Six-week treatment with Ukrain in rats. Part II: Serum levels of gonadal hormones. Drugs Exp Clin Res 1998, 24:301-4.

58. Jagiello-Wojtowicz E, Kleinrock Z, Feldo M, Chodkowska A, Szklarczyk V, Urbanska EM: Six-week treatment with Ukrain in rabbits. Part III: Serum levels of thyroid hormones. Drugs Exp Clin Res 1998, 24:305-8.

59. Jagiello-Wojtowicz E, Kleinrock Z, Chodkowska A, Misztal G, Jagiello G: Preliminary pharmacokinetic studies of Ukrain in rats. Drugs Exp Clin Res 1998, 24:309-11.

60. Gorzelak M, Jablonski M, Piatry 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 Exp Clin Res 1998, 24:313-6.

61. Jablonski M, Gorzelak M, Piatry 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 Exp Clin Res 1998, 24:317-20.

62. Jagiello-Wojtowicz E, Kleinrock Z, Chodkowska A, Szklarzak A, Siemienda E, Gustaw K, et al.: Modification of antinoceptice action of Ukrain by endogenous nitric oxide in the writhing syndrome test in mice. Drugs Exp Clin Res 1998, 24:321-5.

63. Jagiello-Wojtowicz E, Kleinrock Z, Gustaw K: Interaction between Ukrain and Maltrexone in the writhing syndrome test in mice. Drugs Exp Clin Res 1998, 24:327-30.

64. Boyko VN, Zhuluy RB: A comparative evaluation of the influence of the complex drug Ukrain and its components on the effects of radiation. Drugs Exp Clin Res 1998, 24:331-3.

65. Boyko VN, Levshina VA: A study of the influence of a novel drug Ukrain in vitro effects of low-dose ionizing radiation. Drugs Exp Clin Res 1998, 24:339-41.

66. Boyko VN, Zhuluy RB, Legeza VI: 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 Exp Clin Res 1998, 24:343-7.

67. Hurby R: Ukrain: acute toxicity after intravenous, intramuscular and oral administration in rats. Drugs Exp Clin Res 2000, 26:157-61.
BMC Cancer 2005, 5:69

http://www.biomedcentral.com/1471-2407/5/69

97. Aschhoff B: Ukraine treatment in a patient with stage IV neoblastoma. A case report. Drugs Exp Clin Res 1998, 24:243-5.

98. Nowicky JW, Stasienszewska A, Zbroja-Sontag W, Slesak B, Nowicky W, Hiesmayr W: Evaluation of thiophosphoric acid alkaloid derivatives from Chelidonium majus L. ("Ukraine") as an immunostimulant in patients with various carcinomas. Drugs Exp Clin Res 1991, 17:139-43.

99. Danyaz A, Koleschinneg M, Hamler F: Clinical studies of Ukraine in healthy volunteers (phase I). Drugs Exp Clin Res 1992, 18:39-43.

100. Musianowycz J, Judmajar F, Manfreda D, Spangler P, Albrecht H, Hoffmann J, et al.: Clinical studies of Ukraine in terminal cancer Patients (phase II). Drugs Exp Clin Res 1992, 18:45-50.

101. Nowicky JW, Manolakis G, Mejder D, Vatanasapat V, Brzosko WJ: Ukraine both as an anti cancer and immunoregulatory agent. Drugs Exp Clin Res 1992, 18:51-4.

102. Danilos J, Zbroja-Sontag W, Baran E, Kuryloko L, Kondratowicz L, Jurik L: Preliminary studies on the effect of Ukraine (Tris(2-\((Sb-5-Sb, 6b, 12b, 5a, 6, 12)-5, 6, 12, 5b, 6, 12b, 13, 14-hexahydro-13- methyl[1, 3]-benzodioxolo[5, 6-v]-1-3-dioxolo[4, 5-i]phenanthridinium-6-o1\]-Ethaneaminyl) Phosphinesulfide.6HCl) on the immunological response in patients with malignant breast tumors. Drugs Exp Clin Res 1992, 18:55-62.

103. Pongsa P, Wongratroam W, Vatanasapat V, Udomthavornbuk S, Mairieng E, Tangvoralpunchai V, et al.: The effects of thiophosphoric acid (Ukraine) on cervical cancer, stage IB bulky. Drugs Exp Clin Res 1992, 18:57-72.

104. Lohninger A, Hamler F: Chelidonium majus L. (Ukraine) in the treatment of cancer patients. Drugs Exp Clin Res 1992, 18:73-7.

105. Zemskov SV, Iaremchuk Ola, Susak IaM, Denke IaR, Kravchenko OV, Iatyn IM: The initial experience of using the preparation Ukraine in treating cancer patients in Ukraine. Lk Sprava 1996, Jan-Feb:158-61.

106. Nowfeyov LJ, Uglyanitsa KN, Smirnov YV, Karavay AV, Brzosko WJ: Comparative evaluation of blood plasma and tumor tissue amino acid pool in radiation or neoadjuvant preoperative therapeutic of breast cancer with the anthitumor drug Ukraine. Drugs Exp Clin Res 2000, 26:231-7.

107. Uglyanitsa KN, Nefyodov LJ, Karyedova LM, Nowicky JW, Brzosko WJ: Clinical aspects of cancer treatment and new biochemical mechanisms of the drug Ukraine. Drugs Exp Clin Res 2000, 26:239-47.

108. Nefyodov LJ, Uglyanitsa KN, Smirnov YV, Doroshenko YM, Fomin KA, Nowicky JW, et al.: Amino acids and their derivatives in tumour tissue from patients with breast cancer treated with Ukraine. Part VI. Drugs Exp Clin Res 1996, 22:155-7.

109. Uglyanitsa KN, Maciuk JR, Fomin KA, Nowicky JW, Kravchuk RI, Vinogradova LM, et al.: Influence of Ukraine on patients with surgically treated breast cancer. Part IV. Drugs Exp Clin Res 1996, 22:47-53.

110. Fomin KA, Uglyanitsa KN, Nefyodov LJ, Djurd TI, Nowicky JW, Brzosko WJ, et al.: Influence of Ukraine on patients with surgically treated breast cancer. Part III. The immune system. Drugs Exp Clin Res 1996, 22:143-5.

111. Uglyanitsa KN, Fomin KA, Nefyodov LJ, Villkiewich TW, Nowicky JW, Brzosko WJ, et al.: Influence of Ukraine on patients with surgically treated breast cancer. Part II. Hormonal profile. Drugs Exp Clin Res 1996, 22:139-43.

112. Uglyanitsa KN, Fomin KA, Nefyodov LJ, Nowicky JW, Brzosko WJ, Jankowski A: Influence of Ukraine on patients with surgically treated breast cancer. Part I. Clinical and laboratory parameters. Drugs Exp Clin Res 1996, 22:135-8.

113. Neffyodov LJ, Uglyanitsa KN, Nefyodov LJ, Smirnov YV, Brzosko WJ, Karavay NL: New biochemical mechanisms of the anticancer effect of Ukraine in the treatment of cancer of the urinary bladder. Drugs Exp Clin Res 2000, 26:195-9.

114. Uglyanitsa KN, Nefyodov NA, Fomin KA, Brzosko WJ: Ukraine therapy of stage TINOMO bladder cancer patients. Drugs Exp Clin Res 1998, 24:227-30.
117. Uglyanitsa KN, Fomin KA, Nefyodov LI, Nowicky JW, Brzosko WJ, Jankowski A: Influence of Ukrain on patients with surgically treated breast cancer (introductory remarks). Drugs Exp Clin Res 1996, 22:123-5.

118. Uglyanitsa KN, Nefyodov LI, Doroshenko YM, Brzosko WJ: Comparison of the efficacy of different doses of Ukrain in the combined treatment of breast cancer. Drugs Exp Clin Res 2000, 26:201-21.

119. Jadad AR, Moore A, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al.: Assessing the quality of reports of randomized clinical trials: Is blinding necessary. Controlled Clin Trials 1996, 17:1-12.

120. Susak YM, Zemskov SV, Yaremchuk OY, Kravchenko OB, Korsh OB: Comparison of chemotherapy and X-ray therapy with Ukrain monotherapy for colorectal cancer. Drugs Exp Clin Res 1996, 22:115-22.

121. Bondar GV, Borota AV, Yakovets Yl, Zolotukhin SE: Comparative evaluation of the complex treatment of rectal cancer patients (chemotherapy and X-ray therapy, Ukrain monotherapy). Drugs Exp Clin Res 1998, 24:221-6.

122. Zemskov VS, Prokopchuk OL, Susak YM, Zemskov SV, Hodysy YY, Zemskova MV: Ukrain (NSC-631570) in the treatment of pancreatic cancer. Drugs Exp Clin Res 2000, 26:179-90.

123. Uglyanitsa KN, Nefyodov LI, Brzosko WJ: Comparative evaluation of the efficiency of various Ukrain doses in the combined treatment of breast cancer. Report I. Clinical aspects of Ukrain application. Drugs Exp Clin Res 2000, 26:223-30.

124. Zemskov SV, Prokopchuk O, Susak Y, Zemskov S, Tkachchenko O, Hodysy Y, et al.: Efficacy of Ukrain in the treatment of pancreatic cancer. Langenbecks Arch Surg 2002, 387:84-9.

125. Gansauge F, Ramdani M, Pressmar J, Gansauge S, Muehling B, Stecker K, et al.: NSC-631570 (Ukrain) in the palliative treatment of pancreatic cancer. Results of a phase II trial. Langenbecks Arch Surg 2002, 386:570-4.

126. Susak YM, Yaremchuk OY, Zemskov VS, Kravchenko OB, Liepins A, Yatsyk IM, et al.: Randomised clinical study of Ukrain on colorectal cancer. Eur J Cancer 1995, 31:5153. Abstract 733.

127. Jellin JM, Gregory P, Batz F, Hitchens K, et al.: Pharmacist's Letter/ Prescriber's Letter Natural Medicines Comprehensive Database. 3rd edition. Stockton, CA: Therapeutic Research Faculty; 2000.

128. Benninger J, Schneider HT, Schupp M, Kirchner T, Hahn EG: Acute hepatitis induced by Greater Celandine (Chelidonium majus). Gastroenterol 1999, 117:1234-7.

129. Jagiello-Wojtowicz E, Kleinrok Z, Urbanska EM: Ukrain (NSC-631570) in experimental and clinical studies: a review. Drugs Exp Clin Res 1998, 24:213-9.

130. Bone K: Adverse reaction reports: hepatitis induced by greater celandine. Phytother 2000, 5:1-6.

131. Crijus APG, De Smet PAGM, van den Heuvel M, Schot BW, Haagsma EB: Acute hepatitis after use of herbal preparation with greater celandine. Ned Tijdschr Geneeskd 2002, 146:124-8.

132. Hopf G: Ukrain® – Fortschritt oder Rückschritt in der medikamentösen Therapie onkologischer Erkrankungen? Deutsche Zeitschrift für Onkologie 2002, 34:31-6.

Pre-publication history
The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2407/5/69/prepub