



# The Selective Effect of NSC-631570 (UKRAINE)



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**Submission:** August 05, 2017; **Published:** August 28, 2017

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## Opinion

Surgery, chemotherapy and radiotherapy are the three most important types of cancer treatment. However, each of them have their limitations and as well as considerable ad-verse effects. Surgery is the oldest treatment option and, if possible, is still frequently the method of first choice. Unfortunately curative surgical intervention is only possible in few cases; the residual tumour usually remains unrecognized, leading to tumour recurrence and metastazing. Additional treatment then comes into consideration [1,2].

Both radiation and chemotherapy do not have a selective effect against tumour cells, they are themselves carcinogenic (they cause cancer) and mutagenic (they damage chromosomes and change the genetic make-up). It is clear that the problem of the immense adverse effects of chemotherapy cannot be solved in a customary way. This could only be achieved by preparations which only kill cancer cells while leaving healthy cells undamaged, in other words which act selectively against cancer cells.

A new preparation was presented at the 13<sup>th</sup> International Congress of Chemotherapy in Vienna in August-September 1983-thiophosphoric acid derivative of alkaloids from greater celandine (NSC-631570, trade name Ukraine) [3]. The greater celandine (*Chelidonium majus* L.) is a species of the Papaveraceae family. The principal secondary metabolites of the plant are isoquinoline alkaloids; more than 30 were found here. The richest organ is the root, the total content of alkaloids in it reaching 2-3%. The dominant alkaloids of the root are chelidonine and coptisine. The aerial parts contain about 0.5-1.5% alkaloids. The principal base for the whole period of vegetation is coptisine, the representation of other alkaloids substantially changing during the development of the plant. Of non alkaloidal secondary metabolites, esters of caffeic acid have recently been demonstrated in the plant drug. In the past, the drug was used to treat tumours. The extract of alkaloids from the plant is the base of the preparation Ukraine showing immunomodulating activity and being employed in the therapy of different types of carcinomata [4]. The development of this

preparation was the first significant step on the way to solving the problem. In vitro tests showed that after incubation with NSC-631570 normal liver cells and Ehrlich tumour ascitic cells demonstrate different oxygen consumption: after initial increase, oxygen consumption in cancer cells falls to zero whereas oxygen consumption in normal cells returns to normal and the cells remain undamaged [5]. This study brought the first indications that, in contrast to its starting substances thiotepa (a well known cytostatic agent) and greater celandine alkaloids, NSC-631570 is in fact only toxic against cancer cells and not against normal cells. The second indication was provided by clinical use, where NSC-631570 caused no noteworthy side-effects [6]. It improved patients' general condition as well as their immune status which had previously been impaired by chemotherapy [7].

The third indication was provided by a study at the University of Miami, based upon which the therapeutic index of NSC-631570 was calculated to be 1250 [8]. This is unusually high for an anticancer preparation. The therapeutic index is the ratio of the toxic dose to the therapeutic dose and reflects the level of safety of a medicine. The therapeutic index of conventional cytostatic preparations is in the range of 1.4-1.8 meaning that an overdose can have fatal consequences. There is no risk of an over dosage with NSC-631570 on account of its very high therapeutic index of 1250. The development of NSC-631570 was a trail-blazing discovery. The preparation has shown that the problem can be solved and has changed our ideas about healthy and cancer cells.

The presentation at the congress was greeted both by scepticism and great interest. Many reputed research institutes such as the National Cancer Institute (USA), EORTC, the University of Miami, the Rochester University (USA), and University of Tübingen (Germany) began to test the preparation to better explain its unique properties and anticancer potential. In the NCI test model, in contrast to conventional cytostatic preparations which caused the growth inhibition only in some cancer cell lines, like thiotepa inhibited the growth of MLI-09 (non-small lung cancer) and UOK-57LN (renal cancer), NSC-631570 killed all 60 tested cancer cell lines [9], which represent the eight important human tumours, including the cell lines which were

resistant to the strongest cytostatic drug at the time, cisplatin.

Researchers at the University of Natural Resources and Life Sciences, Vienna compared NSC-631570's inhibitive effect on the reproduction of malignant and normal cells. In order to achieve 50% growth inhibition a tenfold concentration of NSC-631570 had to be administered to normal endothelial cells in comparison to a human osteosarcoma cell line. Laser scanning microscopy showed a high capacity to absorb NSC-631570 in malignant cells while absorption in normal cells was considerable lower under the same experimental conditions [10].

In a study of the effect of NSC-631570 on K-562 erythroleucemia cells it was found that the preparation causes bimodal cell death. At lower NSC-631570 concentrations malignant cells die as a result of apoptosis, at higher concentrations the formation of microtubules is prevented and polyploidy occurs [11].

In 1998 a group around Anne Panzer (University of Pretoria, South Africa) proved the selective effect of NSC-631570 on molecular level. Tests on human cervical carcinoma cells HeLa, squamous cell carcinoma WHCO5 and normal equine lung cell lines demonstrated that NSC-631570 is selectively toxic against cancer cells. It causes a metaphase block which is characterised by an abnormal distribution of chromosomes and the formation of micronuclei and results in apoptosis. Normal cells are not influenced in the process [12].

In 2000 in a study of cell proliferation after absorption of BrdU in the cell lines AsPC1, BxPC3, MiaPaCa2, Jurkat and THP-1 and the cell cycle phases – with the help of Giemsa staining, researchers from Ulm found that 10µg/ml NSC-631570 causes a clear accumulation of cancer cells in phase G2/M. Interestingly no difference was seen in the rate of apoptosis in normal peripheral mononuclear cells treated with NSC-631570 compared to those untreated. The blastogenic response of mitogen stimulated lymphocytes was even significantly increased. The authors showed that NSC-631570 blocks pancreas cancer cells in the prophase by inhibiting tubulin polymerization [13]. This study confirmed that NSC-631570 exerts no influence on normal cells.

## References

1. Rebscher H (2002) Off-label use in oncology. Quackery or progress? MMW Fortschr Med 144(41): 25-26.
2. Aschhoff B (2003) Tumor-Arten.
3. Nowicky JW (1983) New Immuno-stimulating anti-cancer preparation "Ukrain". In Nowicky JW (Ed.), 13<sup>th</sup> International Congress of Chemotherapy. 12(5): 33.
4. Taborska E, Bochorakova H, Dostal J, Paulova H (1995) The greater celandine (*Cheli-donium majus* L.)-review of present knowledge. Ceska Slov Farm 44(2): 71-75.
5. Bruller W (1992) Studies concerning the effect of Ukrain *in vivo* and *in vitro*. Drugs Exp Clin Res (18 Suppl): 13-16.
6. Musianowycz J, Judmajer F, Manfreda D, Spangler P, Albrecht H, et al. (1992) Clinical studies of Ukrain in terminal cancer patients (phase II). Drugs under experimental and clinical research, (18 Suppl): 45-50.
7. Danilos J, Zbroja-Sontag W, Baran E, Kurylcio L, Kondratowicz L, et al. (1992) 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-v]-1-3-dioxolo[4,5-i]phenanthridinium-6-ol]-54 Ethaneaminy) Phosphinesulfide. 6HCl) on the immunological response in patients with malignant tumours. Drugs Exp Clin Res 18 Suppl: 55-62.
8. Sotomayor EM, Rao K, Lopez DM, Liepins A (1992) Enhancement of macrophage tumoricidal activity by the alkaloid derivative Ukrain. *In vitro* and *in vivo* studies. Drugs Exp Clin Res 18: 5-11.
9. NCI (1993) NSC 631570: results of the Human Cell Line Screen. In National Cancer Institute, National Institute of Health, Developmental Therapeutics Program.
10. Hohenwarter O, Strutzenberger K, Katinger H, Liepins A, Nowicky JW, et al. (1992) Selective inhibition of *in vitro* cell growth by the anti-tumour drug Ukrain. Drugs Exp Clin Res (18 Suppl): 1-4.
11. Liepins A, Nowicky JW, Bustamante JO, Lam E (1996) Induction of bimodal programmed cell death in malignant cells by the derivative Ukrain (NSC-631570). Drugs Exp Clin Res 22(3-5): 73-79.
12. Panzer A, Seegers J (1998) Ukrain, a semisynthetic alkaloid of *Chelidonium majus*, is selectively toxic to malignant cells by causing a metaphase block which results in apoptosis. In Proceedings of the American Association for Cancer Research. 39 New Orleans, LA, USA.
13. Gansauge F, Ramadani M, Gansauge S, Pressmar J, Muehling B, et al. (2001) Pancreatic Cancer and chemotherapy. New developments from bench to bedside. Progress in Pancreatology and GI-Tract Surgery. In Gastrointestinal Surgery Today the Ulm Surgical School.



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DOI: 10.19080/JTMP.2017.02.555575

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