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EXPERIENCE OF THE USE OF NSC-631570 (UKRAIN) IN THE TREATMENT OF MALIGNANT MELANOMA

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Introduction: Malignant melanoma is one of the most deadly skin cancers. At the early stages of melanoma development the patients are treated surgically, but the advanced disease is virtually incurable. Numerous clinical investigations have been conducted to improve efficiency of melanoma treatment. Nevertheless, biologists and clinicians continue working on new possible methodology of treatment and keep up to search new therapeutic agents as drug resistance is a commonly observed problem. NSC-631570 is an anti-cancer agent created on the basis of alkaloids from the plant *Chelidonium majus*. For more than 20 years NSC-631570 had been used for cancer treatment. Monotherapy and combined application of NSC-631570 are successfully used for the treatment of malignant melanoma since 1996.

Aim: The purpose of this study is to describe the experience of the use of NSC-631570 in the treatment of malignant melanoma and to disclose of some mechanisms of the preparation action.

Materials & Methods: B-16 melanoma cells of C57BL/6 mice were kindly supplied by the Bank of Cell Cultures and Transplantable Experimental Tumors of R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology (Kyiv, Ukraine) MM-4 cells, exhibiting a relatively low metastatic potential, were established from the primary lesion of subcutaneously injected B16 cells. MM-4M2 cell lines established by two sequential passages of lung metastases of MM-4 cells after intravenous injection are highly metastatic. Cells were cultured *in vitro* in Dulbecco's Modified Eagle Medium (DMEM; Sigma, St. Louis, MO, USA) supplemented with 10% fetal calf serum (FCS), penicillin (100 U/ml) and streptomycin (100 µg/ml) at 37°C in 5% CO2. To determine the effects of NSC-631570 on cell viability, cells were treated with NSC6-31570 at the different concentrations (1.6, 3.2, 6.4, 12.5, 25, 50, 100 and 200 µg/ml) for 24hrs and 48hrs periods. Cell viability was determined by MTT test. HMGB1 level in conditioned medium was evaluated by ELISA. TAP mRNA was examined by RT-PCR and TAP protein in ELL Lysates was determined by Western blot.

Results: Treatment of B16 melanoma cells with NSC-631570 at apoptogenic concentrations induced dose-dependent tumor cell death accompanied by dose dependent release of HMGB1, more in high-metastasizing cells. The levels of HMGB1 in the cell probes treated with the drug exhibited strong correlation with the levels of cell death. Author found a significant increase in the number of mRNA for TAP1 in melanoma B16 cells after treatment with NSC-631570 at the non-apoptogenic concentration, whereas only a trace quantity of the TAP1 mRNA was found in untreated cells: Treatment of melanoma B16 cells with NSC-631570 increased expression of mRNA encoding TAP2 by ~3-fold ($p < 0.05$); increase of TAP1-proteins expression was confirmed by Western blot analysis. It is known that correction of TAP1 and/or TAP2 defects in B16 mouse melanoma enhances the cell surface expression of MHC class I molecules and significantly reduces the rate of subcutaneous tumor growth and pulmonary metastatic burden.

Conclusion: Thus, NSC-631570 exhibits powerful therapeutic effect in the treatment of malignant melanoma. The drug not only selectively kills tumor cells but also recovers the role of the dying primary tumor as an effective immunogenic hub.

Recent Publications:

1. Funel N, Costa F, Pettinari L, Taddeo A, Sala A, Chiriva-Internati M and Dalle-Donne I (2010) Ukrain affects pancreas cancer cell phenotype *in vitro* by targeting MMP-9 and intra-/extracellular SPARC expression. Pancreatology, 10(5): 545-552.
2. M Skivka L, G Fedorchuk O, M Susak Y, Y Susak M, M Malanchuk O, P Rudyk M and Nowicky W (2015) Physical activity interferes with the immunomodulatory effect of the antineoplastic drug NSC631570. Current pharmaceutical biotechnology 16(1): 49-59.
3. Rudyk M, Fedorchuk O, Susak Y, Nowicky Y and Skivka L (2016) Introduction of antineoplastic drug NSC631570 in an inpatient and outpatient setting: Comparative evaluation of biological effects. Asian Journal of Pharmaceutical Sciences 11(2): 308-317.
4. Jesionek W, Fornal E, Majer-Dziedzic B, Móricz Á M, Nowicky W and Choma I M (2016) Investigation of the composition and antibacterial activity of Ukrain™ drug using liquid chromatography techniques. Journal of Chromatography A 1429: 340-347.

BIOGRAPHY

Wassil Nowicky is the Director of Nowicky Pharma and President of the Ukrainian Anti-Cancer Institute, Austria. He is the Inventor of the anti-cancer preparation on the basis of celandine alkaloids "NSC-631570". He is the author of over 300 scientific articles dedicated to cancer research. He is a real member of the New York Academy of Sciences, member of the European Union for applied immunology and of the American Association for scientific progress. He is the Honorary Doctor of the Yanka Kupala State University in Grodno, Doctor Honoris Causa of the Open International University on Complex Medicine in Colombo, Honorary Member of the Austrian Society. He has received the award for Merits of National Guild of Pharmacists of America, the award of Austrian Society of Sanitary, Hygiene and Public Health Services and others.

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