

MASHA Project

Ewelina Korczowska, Clinical Hospital of Lord's Transfiguration, Pharmacy Department, University of Medical Sciences in Poznan, Poland

*Research about Environmental Contamination by Cytotoxics and **MA**nagement of Safe **HA**ndling Procedures*

Evaluating environmental contamination with cytotoxic drugs in hospitals is one of the fundamental requirements to ensure the safety of all healthcare professionals. Over the last few years environmental contamination with cytotoxic drugs in hospitals units has been reported in several publications. However, detailed information on surface contamination with antineoplastic drugs in European hospitals in areas where these drugs are handled is still limited. Therefore, the European Society of Oncology Pharmacy (ESOP) undertook the first independent, multi-centre, pan-European study, involving over a dozen hospitals, to measure the current state of cytotoxic contamination in the workplace. This project is called MASHA – Research about Environmental Contamination by Cytotoxics and Management of Safe Handling Procedures.

The study was designed to investigate any possible weak points during drug preparation, transportation and application and during the disposal of medical devices after treatment. Lessons learned would be used to create international guidelines for the handling of antineoplastic drugs. The study was carried out at 15 hospitals in Europe in order to observe a broad variety of procedures and cases.

The study demonstrated the presence of surface contamination in preparation and administration areas in all hospitals, with measurable amounts of at least one agent detected on sampled surfaces. Before the implementation of the ESOP cleaning recommendations, 324 out of 1,595 results were positive (20%). In 11 of 15 hospitals (73%), substances were detected which were not prepared or administered in the sampling day. After implementation, only 14% of samples were positive (226/1639). 69% of wards (9/13) improved or stayed at the same level in the number of positive samples. Contamination was detected mostly on the work surfaces of BSCs/Isolators, floors (in pharmacies and in wards) and the armrests of patient's chairs. The floors at the wards were shown to be the most frequently contaminated (even 42% of samples were positive). The highest numbers of positive results were recorded with *gemcitabine*, *5-fluorouracil*, *cyclophosphamide* and *paclitaxel*, with the highest values for gemcitabine (171 ng/cm²) and 5-fluorouracil (37 ng/cm²).

In summary, the study provided an overview of the local procedures for safe handling of cytotoxic drugs in European hospitals. The results indicate that current cleaning procedures do not remove residual drug from surfaces. With the implementation of the ESOP cleaning recommendations, there were fewer positive samples, lower concentrations detected, and a reduction of the 90th percentile from 0.030 ng/cm² to 0.021 ng/cm².

The EPIC Project – where do we stand?

Dr. Dorothee Dartsch and Klaus Meier, German and European Society of Oncology Pharmacy, Hamburg, Germany

With oral anticancer therapy shifting more responsibility for the correct drug administration towards the patient, strategies are needed by all health care providers of how to support patients in this task. Community pharmacists are easily accessible by patients both at the time of prescription-filling and spontaneously in between and are therefore best positioned to take a part in patient information and education. In the EU project “Empowering pharmacists to improve health care for oral chemotherapy patients: Establishment of a European best-practice model” (EPIC) two established and approved tools – a training programme and a data base on oral anticancer drugs - are being transferred from their country of origin, i.e. Germany, to two partner countries, i.e. Slovenia and Estonia, as a model for future distribution also in other European countries. So far, a questionnaire-based cross-sectional study about the status quo of how and when cancer patients are counseled by pharmacists, about the pharmacists’ knowledge and their confidence when counseling in this specific field was carried out, as well as the translation of the German data base into English language. Translation of the training programme into the Estonian and Slovenian languages is currently under way. The talk will give an overview about the status of EPIC.

ESOP Educational Project Biosimilars - More Education about Biosimilars is urgently required

Prof. Dr. Alain Astier, Hospital Henri Mondor, Service Pharmacie, Creteil, France

Biosimilars are a crucial challenge for pharmacists, now and in the future. But, knowledge about biologics is poorly implemented in the academic pharmaceutical background. However, since pharmacists have to play a key role to explain to the prescribers and patients, sometime strongly influenced by approximate or fake information, the scientific and economical rational to use extensively biosimilars, it is of a key importance to improve these situation.

Thus, ESOP must propose an extensive educational program for oncology pharmacists. This program must be independent of the pharmaceutical industry and cover all the pharmaceutical, clinical and administrative aspects of the biosimilars

Proline oxidase-mediated Apoptosis/Autophagy as a potential Anti-Cancer Strategy

Prof. Dr. Jerzy Palka, Department of Medicinal Chemistry, Medical University of Bialystok, Poland

Ilona Zareba, Arkadiusz Suraczyński, Wojciech Miltyk and Jerzy Palka

Extracellular matrix (ECM) plays important role in modulation of receptor signaling pathways that regulate cell growth, differentiation, gene expression, metabolism of proteins, carbohydrates and lipids. The mechanism of this process undergoes

through interaction of ECM constituents (e.g. collagen) with integrin class of adhesion receptors as well as growth factors interaction with respective receptors. The phenomenon of "cross talk" between these receptors is an important mechanism for the regulation of cellular metabolism. In cancer cells, this mechanism is disturbed. Increased activity of metalloproteinases (MMPs), that usually accompany cancer cell growth and invasion, contribute to extracellular collagen degradation, internalization of collagen degradation products and further hydrolysis to amino acids. Released proline, bearing reducing potential is considered as a stress sensor. For removal of reducing potential proline must be converted into pyrroline-5-carboxylate (P5C) by mitochondrial proline oxidase (POX) or utilized in collagen biosynthesis. POX-dependent conversion of proline into P5C generates ATP for survival autophagy or reactive oxygen species (ROS) that induce apoptosis.

In breast cancer cells with knock-down of POX, inhibition of collagen biosynthesis increases intracellular proline concentration and induces autophagy, while in wild breast cancer cells, such conditions induce apoptosis. In this report we present novel experimental strategy to induce apoptosis in cancer cells and discuss the relevance of this strategy to previous one based on the blocking of epidermal growth factor receptor (EGFR) or integrin receptor signaling. The molecular mechanism of POX-dependent apoptosis involves up-regulation of collagen degradation, increase in prolylase activity, increase in concentration of proline in the cytoplasm, inhibition of collagen biosynthesis and finally utilization of proline in mitochondria by POX, generating ROS-dependent cascade of processes, leading to apoptosis. The studies suggest that availability of proline and high expression of POX facilitate induction of apoptosis while low POX expression may promote pro-survival pathways in breast cancer cells.

No conflict of interest/Nothing to disclose

Action in the EU against Counterfeit Drugs

Prof. Dr. Niels Eckstein, University of Applied Sciences Kaiserslautern, Applied Pharmacy, Campus Pirmasens, Pirmasens, Germany

For many years counterfeit drugs are a huge problem not only in the western hemisphere but specially in so-called third-world countries. Within only the last years, burglary of high-price medicines and their re-entering of the legal pharma-supply-chain has become a growing problem mainly in industrialized countries. As many high-price medicines are biologicals (mainly used in oncology and immunology) patient safety is at high risk.

Within this short talk, we will examine the magnitude of this phenomenon and look at some actions, European and national authorities have taken to fight counterfeit drugs. Some actions are mainly based on a national level but can be escalated to the European dimension, others – especially the guidelines on fighting counterfeit drugs – are already initially based on a European level.

Annotation: the illegal trading of perscription drugs via the internet is only subject to criminal prosecution and, thus, not part of this short talk

High Dose Methotrexate - Specifics of Administration

Jitka Rychlíčková, Hospital Na Bulovce, Clinical Pharmacy, Prague, Czech Republic

The main aim of the therapy by high dose methotrexate is to find a balance between toxicity and efficacy. Methotrexate is eliminated renally by glomerular filtration and by tubular secretion as well. The underlying mechanisms of its nephrotoxicity are direct toxicity, damaging effect of methotrexate crystals and related tubuloglomerular feedback leading to reduction of the glomerular filtration rate.

Toxicity is reduced if optimal excretion is ensured, methotrexate plasma levels being monitored and appropriate folate rescue being administered. The optimal excretion can be reached on three basic levels. The first level is drug interaction avoidance, the second level is prevention of methotrexate accumulation in third space fluids and the third level is hydration and alkalinization.

Mechanisms of particular drug interactions will be presented. Optimal hydration composition, its timing and total volume as well as optimal amount of sodium bicarbonate will be discussed.

Pharmacist's Role in the Prevention and Treatment of Chemotherapy Induced Stomatitis

Franziska Ockert-Schön, General Hospital St. Josef Braunau GmbH, Hospital Pharmacy, Braunau am Inn, Austria

Stomatitis caused by antineoplastic drugs can be a serious side effect that can impact quality of life and adherence of the patient. The incidence of stomatitis of all grades is reported to be 67% in postmenopausal women with hormone receptor-positive, metastatic breast cancer who were treated with everolimus and exemestane.

According to the SWISH-study, this adverse event can be prevented as far as possible by prophylactic use of a “dexamethasone 0.1% mouthwash”. Therefore we developed a formulation for a similar mouthwash, since the exact composition was not described in the publication.

In a first step, a literature search for the crucial chemical and physical characteristics of dexamethasone was performed to determine the galenic properties of the mouthwash. In a next step, we searched for existing similar compositions of mouthwashes, which can be used. The resulting theoretical formulation was tested regarding manufacturing practice.

In contrast to the suspensions described by other colleagues, we were able to create a formulation in which dexamethasone is completely solved. In addition, the viscous consistence contributes to an even moistening of the mouth mucosa.

The mouthwash developed is successfully used on the patients. It shows a good efficacy and a high compliance. Furthermore the manufacturing is simple, so that the prescription is also possible in ambulatory setting.

Non-invasive Screening for Neuroendocrine Tumors. Biogenic Amines as “Gold Standards”

Prof. Dr. Tomasz Bączek, Department of Pharmaceutical Chemistry, Medical University of Gdańsk, Gdańsk, Poland

In recent years, biogenic amines (BAs), such as dopamine, norepinephrine, epinephrine and serotonin have become clinically relevant biomarkers for specific diseases and for monitoring of efficacy of therapy, mostly related to function of central nervous system, inflammation and cancer disease. Additionally, analysis of BAs provides insight into central and peripheral nervous system activity. Since neuroblastoma's (NBL) diagnosis – the most common extracranial tumor of childhood – needs further improvements, the focus is on this type of cancer in the studies.

In order to determine simultaneously biogenic amines, their precursors (tyrosine and tryptophan) and metabolites (5-hydroxytryptophan, 3-methoxytyramine, 5-hydroxyindole-3-acetic acid, vanillylmandelic acid, homovanillic acid, 3,4-dihydroxyphenylacetic acid and L-DOPA), variable microextraction and separation techniques were considered. All proposed methods could be successfully applied for determination of biogenic amines in plasma and urine samples with a reduced volume obtained from hematology pediatric patients.

Advantages and disadvantages of developed approaches are going to be discussed along with the assessment of the level of BAs in clinical samples as the first stage of complex program aiming at construction of sensitive and specific tool currently being during validation on a larger population of children patients.

References

1. L. Konieczna, A. Roszkowska, M. Niedźwiecki, T. Bączek, *Journal of Chromatography A*, 1431 (2016) 111-121.
2. L. Konieczna, A. Roszkowska, A. Synakiewicz, T. Stachowicz-Stencel, E. Adamkiewicz-Drożyńska, T. Bączek, *Talanta*, 150 (2016) 331-339.
3. N. Miękus, P. Kowalski, I. Olędzka, A. Plenis, E. Bień, A. Miękus, M. Krawczyk, E. Adamkiewicz-Drożyńska, T. Bączek, *Journal of Chromatography B*, 1003 (2015) 27-34.
4. N. Miękus, I. Olędzka, A. Plenis, P. Kowalski, E. Bień, A. Miękus, M.A. Krawczyk, E. Adamkiewicz-Drożyńska, T. Bączek, *Journal of Chromatography B*, 1036-1037 (2016) 114-123.
5. N. Miękus, T. Bączek, *Journal of Pharmaceutical and Biomedical Analysis*, 130 (2016) 194-201.

No conflict of interest is applicable.

Laws conducting Safe Working in Germany

Jürgen Barth, University of Gießen, University Hospital, Medical Clinic IV, StiL-Study Group, Gießen, Germany

This is a historical overview about the perception of occupational hazards resulting from the handling of cytotoxic drugs and the resulting juridical provisions for worker protection and safe working in Germany but also in the EU. An extended part deals about therapeutic safety, which is also a field of pharmaceutical responsibility. This was underpinned in 2012 by the revised form of the pharmacy operations regulations (Apothekenbetriebsordnung).

New Way of Decontamination of Cytostatics based on Titania Oxide Nanoparticles

Martin Šťastný, Institute of Inorganic Chemistry AS CR v.v.i, Materials Chemistry Department, Rež, Czech Republic

MARTIN ŠŤASTNÝ¹, VÁCLAV ŠTENGL¹, IRENA ŠTENGLOVÁ NETÍKOVÁ²

¹*Materials Chemistry Department, Institute of Inorganic Chemistry AS CR v.v.i., 25068 Řež, Czech Republic*

²*1st Faculty of Medicine, Charles University in Prague, Ovocný Trh 3-5, 116 36 Praha 1, Czech Republic*

It has been found that some oxides of alkaline earth metals (Mg and Ca) or a light metals (Al and Ti) are generally known that its macrocrystalline form have the ability to respond to standard warfare agents such as sulphur mustard, soman or agent VX [1]. Reaction with the macro-crystalline oxides are slow and decontamination practice unusable. However, if the size of the individual oxide particles decreases in the order of 1-10 nm, it is possible to observe an increase of their specific reactivity. Observed acceleration heterogeneous reaction, which takes place on the surface of the nanocrystals, is explained in particular by increasing the proportion of highly reactive sites, such as the edges and corners of crystals in which the amount of dislocations or defects in shape.

Cytotoxic drugs have also been documented in the urine of health care workers who did not handle cytostatics, but were potentially exposed through fugitive aerosols or secondary contamination of work surfaces, clothing, or drug containers. From this point of view, safe decontamination with using agents, which can cause degradation to define nontoxic products is essential [2], [3].

In this paper, we present a new way of fast and safe surface decontamination of cytostatics drugs, such as cyclophosphamide, ifosfamide, doxorubicin, epirubicin and platinum (from cisplatin or carboplatin) using titania oxide nanoparticles.

Titania oxide nanoparticles were prepared by homogeneous hydrolysis of TiOSO₄ with urea. 1 mL solution of cytostatic drug (2 mg/mL) gets sorbed to the surface of 0.3 g TiO₂ nanoparticles within ~ 5 min. For this reason, titania oxide nanoparticles exhibit an exceptional sorption efficiency towards dangerous cytotoxic drugs.

References

- [1] R. a Fleming, "An overview of cyclophosphamide and ifosfamide pharmacology.," *Pharmacotherapy*, vol. 17, no. 5 Pt 2, p. 146S–154S, 1997.
- [2] H. G. Yang, C. H. Sun, S. Z. Qiao, J. Zou, G. Liu, S. C. Smith, H. M. Cheng, and G. Q. Lu, "Anatase TiO₂ single crystals with a large percentage of reactive facets," *Nature*, vol. 453, no. 7195, pp. 638–641, 2008.
- [3] T. Kosjek and E. Heath, "Occurrence, fate and determination of cytostatic pharmaceuticals in the environment," *TrAC - Trends Anal. Chem.*, vol. 30, no. 7, pp. 1065–1087, 2011.

Strategies to enhance the Adherence of Patients to oral Anticancer Drugs

Katharina Stefanie Ocko, Vienna General Hospital, Pharmacy Department, Vienna, Austria

Oral chemotherapy products are on the rise. Patients are increasingly given the choice of cancer treatment they can take at home. Yet with new opportunities comes new challenges. The ability to self-administer chemotherapy has even more benefit as the course of some therapies has moved from intense short therapies to ones that cover several months to years. As cancer becomes more chronic in nature, this convenience cannot be underestimated for patients living and working while undergoing treatment.

Adherence is often an issue because it is difficult to be certain that patients are taking their medicine or that they are taking them correctly. Drug-drug and food-drug interactions are also important when cancer medications are taken at home.

Patients become non-compliant with their oral cancer care regimen for a variety of reasons including factors such as adverse drug events. Chemotherapy presented in oral form has similar toxicity profiles to infusion forms, and quite often results in serious side effects, which can quickly progress to adverse drug events, resulting in additional medical intervention. Regardless of these reasons, the impact of non-adherence has considerable health and cost implications. Non-adherence and non-compliance results in poorer outcomes for the patient, emergency room visits and hospitalizations as the patient's status deteriorates and side effects turn to adverse events. In short, medication adherence is impacted by a number of complex factors and non-adherence with oral oncology medication can result in reduced quality of care, increased costs for patients and payers and unnecessary suffering for the patient.

So we created patient information leaflets (PILFs) for oral anticancer drugs. Those leaflets contain specific information about the indication, medical conditions, side effects and application instructions. On the front page there is a patient friendly version of the summary of important characteristics and the specific handling of the medication. The back side is created for medical professionals and shows the metabolism, elimination and the drug interaction profile of the cytostatic agent.

Conflicts of Interest: Novartis (speaker's fee)