How to deal with uncertainties regarding the occupational exposure to antineoplastic mixtures. Additive effect should always be considered?

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INTRODUCTION

RISK ASSESSMENT CONSIDERATIONS

The concept that **"safe levels of exposure"** for humans can be identified for individual chemicals is central to the risk assessment of compounds with known toxicological profiles.

Selection of agents for combination chemotherapy regimens involves minimize overlapping of mechanisms of action, antitumor activity and toxicity profile.

Although the toxicological profile and mechanism of action of each individual drug is well characterized, the **toxicological interactions between drugs** are likely, but poorly established at **occupational exposure** context.

The **synergistic nature of interactions may help in understanding the adverse health effects observed in healthcare workers**, where exposure situations are characterized by complex mixtures of chemical agents, and the levels of individual exposing agents are often not sufficiently high to explain the health complaints. However, if a substance is a genotoxic carcinogen, this would be the "lead effect"; normally, no OEL based on a NOEL would be derived and the level would be set so low that it would be unlikely that other effects would be expected.

OCCUPATIONAL EXPOSURE TO ANTINEOPLASTIC AGENTS

Antineoplastic agents are genotoxic agents, meaning that occupational exposure is considered an unacceptable risk, which is considered intolerable, whatever the benefit.

However, and due to the high need of these drugs for cancer treatment their use is unavoidable. Therefore, between the acceptable and unacceptable risks we have to consider the tolerable risk, where a balance has to be found between risk and benefit.

Health care workers (e.g. pharmacists, pharmacy technicians, nursing personnel or environmental services), may be exposed to these agents in the air, on work surfaces, contaminated clothing, medical equipment, patient excreta, and other surfaces since they work in areas where occurs the preparation or administration of these agents.

ACGIH® adopts the approach that the combined effect of a mixture of two or more hazardous substances, which act on the same organ, should be given primary consideration, rather than the effects of each substance individually. In the absence of information of the contrary, **the effects of the different hazards should be considered as additive**.

STUDY DEVELOPED

Recently research project developed in Portuguese Hospitals characterize the occupational exposure to antineoplastic agents and the health effects related. The project aimed to assess exposure of the different risk groups that handle antineoplastic agents in the hospital setting, namely during preparation and administration of these drugs. Here it is presented and discussed the results in a study developed in two hospitals from Lisbon.

MATERIAL AND METHODS

Chemical contamination assessment: Cyclophosphamide (CP), 5-fluorouracil (5FU), and paclitaxel (PTX) were used as surrogate markers for surfaces contamination.

The surfaces were sampled in the first three months of the year 2013 in two different days in each hospital. Data about which drugs were handled was collected.

Surface areas of 100 cm^2, defined by a stainless frame with an internal size of 10×10 cm were wipe-sampled with gauze moistened with ethyl-acetate. The frame was cleaned between each sample, and a new pair of gloves was used for each wipe sample. Wipe samples were taken and analyzed by HPLC-DAD.

Genotoxicity assessment: The peripheral blood was obtained by venipuncture from 46 workers occupationally exposed to antineoplastic drugs, namely: pharmacists, pharmacy technicians and nurses from two hospital pharmacies and three oncology wards; and 46 non-exposed (controls).
Lymphocytes were isolated and cultured for Cytokinesis-Blocked Micronucleus (CBMN) assay.
The studied endpoints were micronucleus, nucleoplasmic bridges and nuclear buds.
Visualization was made with a Leica DM500 microscope with immersion oil and 1000x amplification according to the criteria of classification established and validated by the HUman MicroNucleus (HUMN) International Collaborative Project available in http://www.humn.org.

RESULTS

Hospitals assessed have similar characteristics (Table 1).
Chemical contamination assessment (Table 2) shows that were analyzed a total of 327 samples, of which, it was possible to detect and quantify at least one drug in 121. Contamination by more than one antineoplastic drug occurred mainly in the administration unit. Our results showed contamination by drugs on days when those analytes were not used at all in preparation and administration. This probably results from inappropriate cleaning procedures that can be related with the detergents used and/or the frequency of the this action.
Genotoxicity assessment (Table 3). The data obtained has shown a significant increase of micronuclei in lymphocytes in the exposed group in comparison with controls, on account of genomic instability, as an increased amount of mutations and/or chromosomal aberrations that cytogenetically translate into a greater frequency of changes in chromosome and in the formation of micronuclei.

Table 1 – Main characteristics of the institutions

	Hospital A	Hospital B
Mean number of cancer patients	3429 patients/year	100 patients/day
N.º of nurses in oncology wards	5	5
N.º of pharmacy technicians preparing cytotoxic drugs	10	9
N.º of pharmacists	4	5
Top five drugs	5-FU; CP; Doxorrubicin; Irinotecan; Oxaliplatin	5-FU; CP; Cisplatin; Methotrexate; PTX
Mean n.º of drug preparations/day	60	250
Preparation	Class II BSC in a grade B room (two, hospital A; three, hospital B)	
Personal Protective Equipment	Pharmacy technicians - overshoes, head covering, goggles, mask P2/P3, sterile gown, and sterile gloves (two pairs). Pharmacist and nursing staff - one pair of gloves	

Table 2 – Main results of chemical contamination assessment

Hospitals	CP	5-FU	PTX	Samples with contamination	Contamination with more than 1 drug
A	1/67 (1.5%)	17/67 (25.4%)	17/67 (25.4%)	21/67 (31.3%)	**13/67 (19.4%)**
B	14/260 (5.4%)	18/260 (6.9%)	54/260 (27.3%)	100/260 (38.5%)	**15/260 (5.8%)**
Totals	**15/327 (4.6%)**	**35/327 (10.7%)**	**71/327 (21.7%)**	**121/327 (37%)**	**28/327 (8.6%)**

Table 3 – MN, NPB and NBUD in the two groups. Association between exposure and genotoxicity biomarkers

	MN in BN Mean ± S.E. (range)	NPB Mean ± S.E.(range)	NBUD Mean ± S.E. (range)
Exposed	9.83±1.28 (1-58)*	0.65±0.14 (0-3)*	2.43±0.37 (0-11)*
Controls	5.09±0.89 (0-34)*	0.11±0.05 (0-1)*	1.37±0.32 (0-13)*
OR (95%CI)	6.667 (2.369-18.76)	5.770 (1.924-17.307)	2.893 (1.135-7.373)

Abbreviations: MN - Micronucleus ; BN - NPB – Nucleoplasmic Bridges; NBUD – Nuclear Buds. *Mann-Whitney test (p-value<0.001)

CONCLUSIONS

Considering that nowadays the combined therapy with two or more agents is increasing, it is important to understand that, although the drugs dose is lower, the effects of the mixtures should be investigated as additives, and further studies are required in this field. Results obtained claimed attention also to the fact that exposure is probably occurring as a mixture and there are procedures that promote this.

As newly developed antineoplastic drugs are designed and introduced, in order to attack specific intracellular targets, their harmful effects could easily "escape" from detection by most standard endpoints. The CBMN should be used to accurately evaluate cytogenetic outcomes of such exposures. Its value in the assessment of genotoxic damage among occupationally exposed personnel was also confirmed in this study.

These studies are of particular interest to healthcare professionals who has the potential to come in contact with these drugs. Countries like Portugal, which witnessed an increase in hospital production in the field of oncological diseases since 2007, resulting in an intensification of occupational exposure to antineoplastic drugs of health care workers in hospital cytotoxic circuit, consequence partly by the *National Health System* hospital centralization process, should be aware to this problem.

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