

# Knowledge and Attitude about Exposure to Cytotoxic Drugs in Oncology Nurses

Hosein Rafie Manesh<sup>1</sup>, Zahra Panjali<sup>2,3\*</sup>, Farah Khani<sup>4</sup>, Majid Habibi-Mohraz<sup>5</sup>, Maryam Borhani<sup>6</sup>

<sup>1</sup> Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran • <sup>2</sup> Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran • <sup>3</sup> Department of Occupational Health Engineering, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran • <sup>4</sup> Nursing, Health and Nursing, Faculty of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran • <sup>5</sup> Department of Occupational Health Engineering, School of Health, Hamedan University of Medical Sciences, Hamedan, Iran • <sup>6</sup> Department of Occupational Health Engineering, Faculty of Health, Iran University of Medical Sciences, Tehran, Iran • \*Corresponding author: Zahra Panjali, Email: panjali@sbmu.ac.ir Tel: +98-912-7971196

## Abstract

**Background:** One of the most common hazards among the nurses is exposure to harmful chemicals. Cytotoxic drugs are among highly hazardous substances in the healthcare centers that can lead to DNA damage and cancer development. Therefore, this study was conducted to investigate the knowledge and attitude of nurses working in the oncology departments of Tehran hospitals regarding the risks and safety measures related to handling of cytotoxic drugs. **Methods:** In this cross-sectional study to develop an instrument, a questionnaire on knowledge and attitude regarding exposure to cytotoxic drugs was translated into Persian language and its validity and reliability evaluated and confirmed. The questionnaire was administered to 111 nurses working in 10 oncology departments (eight hospitals of Tehran) selected by random multistage sampling. For instrument validation, CVI and Cronbach's alpha were used. Descriptive analyses were done to analyze field work data. **Results:** In this study, 22 men (19.8%) and 89 women (80.2%) participated. The mean age of participants was 33.6 (SD 8.6) years. Only 45% of participants constantly used gloves when handling drugs. Results indicated that 54.1% of participants had accidental exposure to cytotoxic drugs, 22.5% of who reported their exposure as being acute. Only 12.6% of participants reported that their efforts to reduce the risks of exposure as effective. At least 84.4% of the nurses had been trained in the handling of cytotoxic drugs, 54% of whom reported that the training was not effective. **Conclusion:** While confirming the reliability and validity of the instrument, this study showed that the training on improving the safety of the personnel is ineffective and insufficient, and most staff are at risk of direct and indirect exposure to cytotoxic drugs. Further the immunization of the workplace and the preparation and proclamation of safety and health protocols for handling of these drugs or attending their storage places can be beneficial.

**Keywords:** Validity; Reliability; Cytotoxic drugs; Knowledge and Attitude

## Introduction

Cytotoxic drugs can eliminate the rapid growth and division of cancer cells. Meanwhile these drugs can affect the growth of other fast-separating cells such as hair follicles and gastrointestinal epithelial cells. Cytotoxic drugs are used in various

healthcare and laboratory services, production laboratories, and veterinary research and clinics. The most important application of these drugs is their use in the chemotherapy process in healthcare centers, but they have also been recently used to treat non-cancer

**Citation:** Rafie Manesh H, Panjali Z, Khani F, Habibi-Mohraz M, Borhani M. Knowledge and Attitude about Exposure to Cytotoxic Drugs in Oncology Nurses. Archives of Occupational Health. 2019; 3(3): 371-9.

**Article History:** Received: 13 April 2019; Revised: 19 May 2019; Accepted: 10 June 2019

**Copyright:** ©2019 The Author(s); Published by Shahid Sadoughi University of Medical Sciences. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

diseases, including multiple sclerosis, psoriasis, systemic lupus erythematosus, and rheumatoid arthritis in children and adolescents.<sup>1</sup> It should not be forgotten that cytotoxic drugs, while destroying cancer cells, can also damage normal cells.<sup>2</sup> The action mechanism of cytotoxic drugs is to damage cell DNA and interfere with their repair process.<sup>3</sup>

Because DNA damage caused by these drugs is non-selective, they can produce serious adverse effects on the normal cells of the body, as the resistance of most normal cells to these drugs is lower than that of the cancer cells.<sup>4, 5</sup> With extensive studies in this field, the effects of cytotoxic drugs have become relatively known.<sup>5, 6</sup> These drugs also have long-term mutagenic, teratogenic and carcinogenic effects in addition to acute harmful effects (e.g., irritation of the skin, eyes, mucous membranes and nose, vomiting, hair loss).<sup>7, 8</sup> Epidemiological studies have shown that secondary cancers are likely to develop in patients treated with cytotoxic drugs. The International Agency for Research on Cancer has classified 11 anticancer drugs into group 1 (human carcinogens), 12 drugs into group 2A (possibly carcinogenic) and 11 drugs into group 2B (potentially carcinogenic).<sup>7-9</sup>

Therefore exposure to drugs can be a serious issue especially in employees including physicians, nurses and other healthcare providers. Occupational exposure to anticancer drugs has been raised since 1970 as an important health risk for people working in various healthcare departments involved in the preparation and administration of these drugs. Studying the mutagenicity of cytotoxic drugs, Flack was first to notice the presence of cyclophosphamide (CP) in the urine of nurses handling these drugs in the clinic.<sup>9-11</sup> Besides, studies have reported the exposure to cytotoxic drugs and even related lesions or garbage.<sup>1</sup> In previous studies, it has been determined that the staff of the healthcare centers are exposed to cytotoxic substances when preparing and administering the drugs, taking care of the patient, managing the wastewater, disposing of the garbage or handling patient biological and

excretory substances.<sup>1, 12-14</sup>

Throughout the process of preparing and administering drugs, pharmacists who prepare these drugs and nurses who are involved in their preparation and administration, are two main groups at risk of exposure to these drugs. In addition, physicians, operating room staff, and nurse assistants and logistics staff can also be at risk.<sup>9</sup> Following the publication of Falck's first report on the potential risks of anticancer drugs, several studies have been conducted for biological and environmental monitoring of these drugs in different countries. Overall, the results of these studies indicate that genetic damage due to exposure to anticancer drugs exists in hospital staff who use no or inadequate protective equipment.

In some studies, the levels of the anticancer drugs CP, ifosfamide, 5-fluorouracil, methotrexate and platinum-induced cisplatin and carboplatin have been determined in the urine of individuals exposed to these drugs in hospitals and oncology departments. The results of these studies indicate that despite the use of personal protective equipment (PPE) and appropriate control equipment, people have received high levels of these drugs.<sup>15-21</sup> Although the risk of occupational exposure to anticancer drugs has been highlighted since 1970 and many studies have been conducted to evaluate exposure risk and to identify ways to reduce exposure to these drugs, few studies have been conducted in Iran and adequate evidence is not available regarding safety and integrated protocols for the protection of treatment staff, training on methods of controlling exposure to drugs, the need for PPE and the improvement of the environment of handling drugs. However, many centers have codified and made available certain guidelines to their staff. In this study conducted in the staff of the oncology departments, their knowledge and attitudes regarding the handling and management of cytotoxic drugs was studied.

## Methods

The present study was a cross-sectional, analytical study aimed to investigate the knowledge and attitudes of the staff of the departments involved in the preparation and administration of cytotoxic drugs. To this end, 111 nurses working in 10 oncology departments (eight hospitals of Tehran) were enrolled in the study by random multistage sampling. To this end, a questionnaire on knowledge and attitude regarding exposure to cytotoxic drugs<sup>22</sup> was used. Because the questionnaire was adapted from the study of Teschke et al. and its Persian version was not available, in addition to measurement of knowledge and attitude of the staff, a psychometric evaluation of the instrument was also done.

### Questionnaire items

The questionnaire was completed by all participants in this study. Participants were head nurses and nurses working in the oncology departments of eight hospitals in Tehran. This questionnaire consists of 44 items on nine domains consisting of:

1. Personal information;
2. handling cytotoxic drugs;
3. risks and control measures;
4. Staff viewpoints about exposure and risk;
5. Protection and organizational communication in the workplace;
6. Training on cytotoxic drugs;
7. The general stress of the employee's job,
8. Hand washing and PPE; and
9. Previous exposure to cytotoxic drugs.

### Translation

For the translation of the instrument into the Persian language, the questionnaire was translated using the forward and backward translation method. In this method, the questionnaire was first translated into Persian by two English language experts independently. Then the Persian version was back translated into English by an English language expert

who was not involved in translating the questionnaire into Persian. Finally, two questionnaires were compared and after making the necessary corrections and editions, the final Persian duplicate of the questionnaire was prepared to investigate its content and face validity.

### Determination of questionnaire reliability indices

To investigate the reliability of the questionnaire, two indices internal consistency and external consistency were used. For internal and external consistency, the Cronbach's alpha coefficient and the test-retest reliability estimate for 2-week interval were used, respectively. To determine the reliability, 38 individuals were included in the study, including expert and knowledgeable individuals. ICC (Interclass Correlations) was also used to assess the reliability of the questionnaire.

### Instrument validation

To validate the instrument, two indices face validity and content validity were used. To investigate face validity in order to eliminate the remaining drawbacks, the viewpoints of five content experts and five informed individuals were used. Besides, in a pilot study the viewpoints of 10 individuals from the target population were also elicited. In order to investigate content validity, after translating the questionnaire, three groups including 10 experts on the content of the studied subject, five individuals from the target population, four lay experts and one methodologist were hired. Content validity was investigated using three indices relevancy, clarity, and comprehensiveness. Finally, the I-CVIs (Item Content Validity Indexes) item appropriateness and item transparency and the S-CVIs (Scale Content Validity Indexes) scale appropriateness, scale transparency, and scale comprehensiveness were presented.

### Data analysis

To conduct data analysis, SPSS software version 18 was used. To this end, descriptive statistics including mean and standard deviation as well as

reliability and validity indices including CVI (Content Validity Index), ICC and Cronbach's alpha were used. In all statistical tests confidence interval was considered to be 95% with a significance level of 0.05.

### Result

In this study, data from 111 individuals were analyzed, of whom 89 (80.2%) were female. The mean age of our participants was 33.6 (SD 8.6) years. Of the participants, 92 (82.9%) were working as nurses and 10 (9.0%) as head nurses in the studied departments. The study was conducted in eight hospitals in Tehran. Data were collected from 10 hospital departments where the transport, preparation or administration of cytotoxic drugs were accomplished. All participants in this study were working on regular (daily) shifts in places where cytotoxic drugs were transported, prepared or administered. Of the participants, 96 (86.5%) were involved in the transport, preparation and administration of cytotoxic drugs as part of their routine tasks and had an average history of 4.4 (SD 4.2) years of working in this field. Of these individuals, 40.6% spent at least 25-50% of their work time doing their respective tasks.

Instrument psychometric evaluation and validation Few Persian duplicates of the instrument were provided to experts. After their viewpoints were reviewed, some preliminary grammatical corrections were made and some statements were reworded, the duplicates were returned to the experts and the results of their final evaluations were analyzed using a Likert scale. Table 1 shows the results of the analyses on reliability and repeatability, as well as on the three indices item clarity, item appropriateness and item comprehensiveness. The Waltz and Basel Validation Index<sup>23</sup> as a general CVI for the instrument indicated that all items could be used and no items needed to be deleted. Based on the analysis of the reliability of the items, it was found that all domains had an alpha coefficient of  $> 0.672$ .

### Knowledge and attitude

Next after validating the instrument, the Persian duplicates of the questionnaire were distributed among the participants and the data drawn from them analyzed. The results showed that 67 (69.8%) participants who were involved in the transportation, preparation and administration of cytotoxic drugs as part of their routine tasks used gloves during direct transport, preparation and administration of the drugs. Of all the participants, 50 (45.0%) constantly used gloves in places where cytotoxic drugs were transported, prepared or administered.

#### Exposure to cytotoxic drugs

According to participants' statements, during handling of cytotoxic drugs, 60 (54.1%) had direct and accidental exposure to these drugs. Twenty five (22.5%) participants assessed the severity of their exposure to cytotoxic drugs as extremely high and estimated average exposure for exposed individuals at 61.9 (range; 0-100). Sixty eight (61.3%) participants reported exposure to cytotoxic drugs as being extremely hazardous, and estimated the average score on the drugs hazard at 87.4 (range; 0-100). In addition, efforts to reduce the risk of drug exposure and the success of these efforts were assessed as being extremely high by 37 (33.3%) and 14 (12.6%) of the participants, respectively. Twenty seven (20.7%) participants reported physical damage as a result of exposure to cytotoxic drugs Figure 1.

#### Risk and exposure

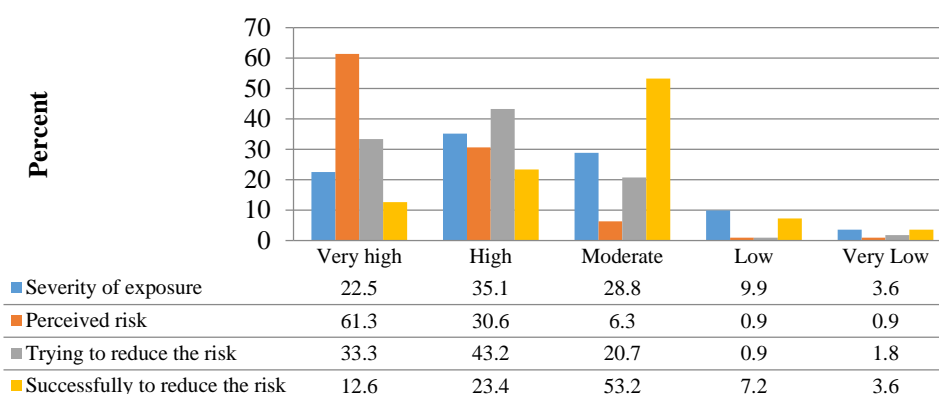
The risk and exposure to cytotoxic drugs were assessed by 5 items rated on a 5-point Likert scale ranging from 1 (low exposure and risk) to 5 (high exposure and risk). The scores of the respondents could therefore range from 5 (minimum risk and exposure) to 25 (maximum exposure and risk). In this study, the minimum and maximum scores were 6 and 21, respectively, and the mean score on individual exposure and risk was 15.1 (SD 2.3) Table 2. Of the total participants, 40.5% reported current safety measures to reduce contamination due

to cytotoxic drugs as being (relatively) appropriate, and 43.2% were sure that they could handle

cytotoxic drugs safely and without incidence of any complication to them.

**Table 1.** Results regarding the questionnaire's reliability and validity

Domain	Internal	Repeatability	Content validity		
	Consistency	y	Transparency	Approximations	Comprehensiveness
Exposure to cytotoxic drugs	0.841	0.903	0.934	1	1
Attitude regarding exposure and risk	0.681	0.742	0.986	0.986	0.933
Protection and organizational communication in the workplace	0.801	0.867	0.972	0.986	0.866
Training on cytotoxic drugs	0.727	0.934	0.977	0.988	1
Stress due to handling cytotoxic drugs	0.738	0.919	0.865	0.850	0.666
Hand washing and personal protective equipment	0.672	0.626	0.947	0.832	0.867



**Figure 1.** Distribution of responses related to attitude towards risks and control measures

**Table 2.** The frequency of answers to items on exposure and exposure risk

Item	Absolutely agree	Agree	No idea	Disagree	Absolutely disagree
1. The risk of my exposure to cytotoxic drugs in the hospital is very low	*(5.4)6	(9.0)10	(14.4)16	(50.5)56	(20.7)23
2. I'm afraid to work with cytotoxic drugs or work near these drugs.	(21.6)24	32.4)36	(23.4)26	(18.0)20	(4.5)5
3. The safety measures at your workplace are appropriate for reducing contamination due to the cytotoxic drugs.	(7.2)8	(33.3)37	(19.8)22	(26.1)29	(13.5)15
4. My colleagues safely handle cytotoxic drugs	(5.4)6	(43.2)48	(21.6)24	(27.9)31	(1.8)2
5. I am sure that I can work safely in all conditions and in all places where there is a risk of exposure to cytotoxic drugs such as spills, leaks, contaminated urine and vomiting of patients.	(3.6)4	(39.6)44	(18.9)21	(29.7)33	(8.1)9

\* Number (percentage)

**Table 3.** The frequency of answers to items on job stress

Item	Absolutely agree	Agree	No idea	Disagree	Absolutely disagree
1. This job forces me to work very quickly.	(40.5)45	(41.4)46	(11.7)13	(5.4)6	(0.9)1
2. In this job, I'm asked to do a lot of work.	(28.8)32	(50.5)56	(10.8)12	(8.1)9	(1.8)2
3. In this job, I have enough time to do my job and handle my duties.	(9.0)10	(18.9)21	(20.7)23	(38.7)43	(12.6)14
4. In my current job, there is not much violence, conflict or encounter.	(7.2)8	(22.5)25	(36.0)40	(24.3)27	(9.9)11



Protection and organizational communication in the workplace

Protection and organizational communication in the workplace was investigated by 5 items rated on a 5-point Likert scale ranging from 1 (low protection and organizational communication) to 5 (high protection and organizational communication). Therefore, the scores attained by the respondents could range from 5 (minimum risk and exposure) to 25 (maximum exposure and risk). In this study, the minimum and maximum scores were 5 and 22, respectively, and the mean score on items related to protection and organizational communication was 12.8 (SD 3.9).

### Training on cytotoxic drugs

According to the obtained data, receiving training on health and safe handling of cytotoxic drugs was once every six months for 44 (40.0%) participants, once every year for 47 (42.7%) and once every few years for 10 (9.1%), and 9 (8.2%) reported that they had not received any training. It was also found that of those who received the training, 88 (85.4%) received training on harmful effects of exposure, 81 (84.4%) were trained in the types of surfaces, objects and contamination remnants, 86 (92.5%) in safety measures in exposures and 91 (92.9%) in PPE. According to the statements of 55 (54%) participants, training on cytotoxic drugs was not adequate to protect them.

### Job stress

The stress due to handling of cytotoxic drugs was investigated by 4 items rated on a 5-point Likert scale ranging from 1 (low stress) to 5 (high stress). Therefore, the scores attained by the respondents could range from 4 (minimum stress) to 20 (maximum stress). In this study, the minimum and maximum scores were 5 and 20, respectively. The mean score on items related to protection and organizational communication was 14.5 (SD 1.3) Table 3.

## Discussion

The present study was aimed to improve the safety

in the staff of hospital oncology departments. According to the previous studies, it has been determined that some of these departments in the hospitals do not take adequate protective measures and the risk of exposure of their staff to antineoplastic drugs and the resulting injuries are high. The results of our study showed that the staff were also aware of these hazards and, in some cases, had taken certain corrective measures in this regard. However, subsequent risks and employment in this area remain to be worrying and stressful for them. In this study, various psychometric properties and validity of the tool were studied. Experts on this field were physicians, nurses working in the oncology departments, methodologists and health professionals.

First, the instrument needed to be validated. Therefore, with the aim of investigating the appropriateness of instrument or the need for its revision, face validity was investigated, for which the viewpoints of experts were elicited. The results showed that the CVI was higher than 0.83 for all the items and therefore all the items with a score of over 0.79 were maintained.<sup>23</sup> The ICC for 38 participants, which indicates the repeatability or external reliability of the questionnaire (0.6866-0.934), was approved for all domains of the questionnaire. The results of our study showed that only 45% of the staff constantly used gloves when they attended cytotoxic drugs storage and administration rooms. Besides, 69.8% of our participants reported to use gloves when handling or preparing the drug; in other words, roughly 30% of them did not pay adequate attention to this issue. Our results also showed that 54.1% of participants had at least one accidental and unintentional exposure to these drugs, 25% of whom assessed their exposure level as being extremely high. According to our participants' answers to the item to estimate the amount of their exposure to cytotoxic drugs (range; 0-100), their average exposure was 61.9. In a national study in Japan, 100% of pharmacists and treatment staff who confronted cytotoxic drugs used masks,

gloves and gowns, 37% used helmets and 25% used eye protectors.<sup>24</sup> Over half of our participants evaluated the exposure to cytotoxic drugs as being extremely hazardous so that 61.3% of them considered the risk of exposure to cytotoxic drugs as extremely high and estimated the average exposure risk at 87.4 (out of 100). 33.3% of the participants stated that they took corrective actions to reduce risks, only 12.6% of whom considered their or their respective organization's efforts to be effective in reducing exposure risk. Some (40.5%) participants also stated that in their department corrective and safety measures were sufficient to control the risks.

Overall, corrective measures are required in such departments, and proper measures and guidelines can reduce individual risks and exposure. Studies have been conducted on control measures and safety interventions that have reduced staff exposure in the long term. In this regard, a study was conducted to investigate the impacts of a control measure, namely, PIVAS (pharmacy intravenous admixture service surveillance) on the decrease of cytotoxic drug exposure and consequently the incidence of injury in the staff of two hospitals in China. The results of that study showed that after the installation of PIVAS and two years after the intervention blood cell count and renal and pregnancy-related problems improved in nurses.<sup>25</sup> In a 10-year study in 5 hospitals in Italy, the implementation and use of the guidelines for proper transport and cleansing of antineoplastic substances decreased positive urine tests from 30% to 0%.<sup>26</sup>

Similarly in another study, analysis of surface samples and pads attached to the staff was found to be less than the detectable limit of the LC-MS device. That study also confirmed that control measures and the implementation of safety guidelines reduced the leakage of pharmaceutical dust and as a result staff exposure approached zero level.<sup>27</sup> In the domain of protection and organizational communication in the investigated departments, the support and organizational relationship did not fully cover all staff,

and staff were concerned that if problems arose, they would not have the necessary support and that managers and supervisors of the departments would not give priority to addressing relevant issues and safety measures in the departments.

In this domain, the score attained was 12.8 (of the total score 25). Planning for and establishing an appropriate supportive system as well as better communication between organizational ranks can greatly improve this issue, as in the study of Fries in the United States (Michigan hospitals) organizational support and increasing the staff when the workload was heavy, reduced the amount of drug exposure in the staff.<sup>28</sup> Our analysis of the training domain showed that 82.7% of the staff had been trained at least once a year and been taught in the cleansing methods of the surfaces, transporting drugs and taking necessary protective measures in handling drugs, and were familiar with the related risks.

However, 54% of them reported that these trainings were not adequate to protect them against the risks and could not control the risks. Therefore, the need for a revision of the training status is needed, and changing the current training methods can prepare individuals to deal with risks more effectively than ever. The lack of adequate knowledge on this domain among staff has also been reported in other studies. A study of knowledge on safety measures in confronting anticancer drugs in a hospital in France showed that 89% of the staff did not have adequate knowledge to deal with the hazardous conditions and to handle drugs safely. Only 44% of the staff used the wet wiping for cleansing and 11% did not adopt a specific cleansing method. Kieffer et al. have therefore recommended to adopt a more effective and comprehensive educational system.<sup>14</sup> Meanwhile, lack of knowledge about the ways of confronting risks and their incidence can cause numerous worries in staff leading to higher stress for them, so that in addition to the complications due to toxic substances, these substances also lead to mental complications and

inefficiency in department staff. Therefore, training on safe working and related guidelines not only obviates additional worries but also improves the safety and health of staff. In the study of Keat et al., it was found that training on safety and safe handling of antineoplastic drugs improved the knowledge of staff in the department [confirmed by the increase of score from 7.5 to 15.5 (out of 20)]. Statistical analysis indicates that these changes are significant ( $p < 0.001$ ). The training provided in this study improved the safety behaviors of staff especially those related to drug transport and PPE use.<sup>13</sup>

### Conclusion

According to the results, it can be argued that the studied questionnaire developed to investigate the knowledge and attitudes of nurses confronting cytotoxic drugs is reliable, valid and repeatable. Furthermore, the content validity of the questionnaire suggests that all domains have clarity, appropriateness and comprehensiveness; therefore, the levels of knowledge and attitudes of staff regarding occupational exposure to antineoplastic drugs can be investigated using this preliminary assessment tool. It can also be used to qualitatively measure drug exposure, risk level, stress, organizational communication for changing risks and staff training, and therefore achieve a relatively comprehensive assessment of the condition. One limitation of our study was lack of cooperation of all staff with completing the questionnaire. It is also suggested that in future studies, the level of personal exposure of staff and the methods of organizational management in control measures be taken into account and the results regarding the two domains be compared. It is also advisable to do control interventions and laboratory measurements to determine individual scale impacts and exposure.

### Acknowledgement

The present study was supported by the Student Research Committee of Tehran University of Medical

Sciences (grant no.: 27575-61-04-93). The research team also wish to acknowledge the assistance of supervisors and staff of the oncology departments of Imam Hossein, Shahadaye Tajrish, Taleghani, Khatamolanbia, Chamran, Bahman, Hazrat Rasool and Imam Khomeini Hospitals in doing this study.

### References

1. Workplace Health and Safety Queensland. Guide for handling cytotoxic drugs and related waste. Queensland: office of industrial relation; 2017.
2. Gohari AR, Saeidnia S, Gohari M, Moradi - Afrapoli F, Malmir M, Hadjiakhoondi A, et al. Shrimp Cytotoxicity of Some Medicinal Plants Belongs to Lamiaceae, Asteraceae, Rosaceae and Boraginaceae Families. *Medicinal Plants*. 2009;8(29):87-181.
3. Cometta T, Padua L, Testa A, Ievoli E, Festa F, Tranfo G, et al. Molecular biomonitoring of a population of nurses handling antineoplastic drugs. *Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis*. 2008;638(1-2):75-82.
4. Turci R, Sottani C, Ronchi A, Minoia C. Biological monitoring of hospital personnel occupationally exposed to antineoplastic agents. *Toxicology Letters*. 2002;134(1-3):57-64.
5. Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, et al. Drug resistance in cancer: an overview. *Cancers*. 2014;6(3):1769-92.
6. Connor TH, McDiarmid MA. Preventing Occupational Exposures to Antineoplastic Drugs in Health Care Settings. CA: *Cancer Journal for Clinicians*. 2006;56(6):354-65.
7. Baker GH. Invited review: Psychological factors and immunity. *Psychosomatic Research*. 1987;31(1):1-10.
8. Greene MH, Harris EL, Gershenson DM, Malkasian GD, Melton LJ, Dembo AJ, et al. Melphalan may be a more potent leukemogen than cyclophosphamide. *Annals of internal medicine*. 1986;105(3):360-7.
9. Alert N. Preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. NIOSH: Department of health and human services CDC; 2004.
10. Donner AL. Possible risk of working with antineoplastic drugs in horizontal laminar flow hoods. *American Journal of Health-System Pharmacy*. 1978;35(8):900.
11. Ng LM. Possible hazards of handling antineoplastic drugs. *Pediatrics*. 1970;46(4):648.
12. Mason HJ, Morton J, Garfitt SJ, Iqbal S, Jones K. Cytotoxic drug contamination on the outside of vials delivered to a hospital pharmacy. *Annals of Occupational Hygiene*. 2003;47(8):681-5.
13. Keat CH, Soaid NS, Yun CY, Sriraman M. Improving Safety-Related Knowledge, Attitude and Practices of Nurses Handling Cytotoxic Anticancer Drug: Pharmacists Experience in a General Hospital, Malaysia. *Asian Pacific Journal of Cancer Prevention*. 2013;14(1):69-73.
14. Kieffer C, Verhaeghe P, Lagrassa S, Grégoire R, Moussaoui Z, Casteras-Ducros C, et al. Preventing the contamination of hospital personnel by cytotoxic agents: evaluation and training of the para-professional healthcare workers in oncology units. *European*



- journal of cancer care. 2015;24(3):404-10.
15. Pethran A, Schierl R, Hauff K, Grimm C-H, Boos K-S, Nowak D. Uptake of antineoplastic agents in pharmacy and hospital personnel. Part I: monitoring of urinary concentrations. *International archives of occupational and environmental health*. 2003;76(1):5-10.
16. Ensslin AS, Pethran A, Schierl R, Fruhmann G. Urinary platinum in hospital personnel occupationally exposed to platinum-containing antineoplastic drugs. *International archives of occupational and environmental health*. 1994;65(5):339-42.
17. Ensslin AS, Huber R, Pethran A, Römmelt H, Schierl R, Kulka U, et al. Biological monitoring of hospital pharmacy personnel occupationally exposed to cytostatic drugs: urinary excretion and cytogenetics studies. *International archives of occupational and environmental health*. 1997;70(3):205-8.
18. Minoia C, Turci R, Sottani C, Schiavi A, Perbellini L, Angeleri S, et al. Application of high performance liquid chromatography/tandem mass spectrometry in the environmental and biological monitoring of health care personnel occupationally exposed to cyclophosphamide and ifosfamide. *Rapid communications in mass spectrometry*. 1998;12(20):1485-93.
19. Evelo CTA, Bos RP, Peters JGP, Henderson PT. Urinary cyclophosphamide assay as a method for biological monitoring of occupational exposure to cyclophosphamide. *International archives of occupational and environmental health*. 1986;58(2):151-5.
20. Sessink PJM, Timmersmans JL, Anzion RBM, Bos RP. Assessment of occupational exposure of pharmaceutical plant workers to 5-fluorouracil. Determination of  $\sigma$ -fluoro- $\beta$ -alanine in urine. *Occupational and Environmental Medicine*. 1994;36(1):79-83.
21. Mader RM, Rizovski B, Steger GG, Wachter A, Kotz R, Rainer H. Exposure of oncologic nurses to methotrexate in the treatment of osteosarcoma. *Archives of environmental health: An International Journal*. 1996;51(4):310-4.
22. Teschke K, Chu W, Hon C-Y. *Healthcare Workers and Antineoplastic Drugs: Identifying the Determinants of Exposure and Current Challenges to Reducing Exposure*. British Columbia: WorkSafeBC; 2012.
23. Ghasemi E, Janani L, Dehghan Nayeri N, Negarandeh R. Psychometric Properties of Persian Version of the Competency Inventory for Registered Nurse (CIRN). *Iran Journal of Nursing*. 2014;27(87):1-13.
24. Shirakawa T, Hara T, Hata K, Hata K, Suetsugu K, Kakimoto H, et al. Analysis of a Questionnaire Survey regarding Current Conditions against Exposure to Anticancer Drugs and Reports of Cancer Chemotherapy at Outpatient Departments in Japan. *Pharmacology & Pharmacy*. 2017;8(05):140.
25. Zhang X, Zheng Q, Lv Y, An M, Zhang Y, Wei Y, et al. Evaluation of adverse health risks associated with antineoplastic drug exposure in nurses at two Chinese hospitals: The effects of implementing a pharmacy intravenous admixture service. *American journal of industrial medicine*. 2016;59(4):264-73.
26. Sottani C, Porro B, Comelli M, Imbriani M, Minoia C. An analysis to study trends in occupational exposure to antineoplastic drugs among health care workers. *Chromatography B*. 2010;878(27):2593-605.
27. Sottani C, Porro B, Imbriani M, Minoia C. Occupational exposure to antineoplastic drugs in four Italian health care settings. *Toxicology letters*. 2012;213(1):107-15.
28. Friesen CR, Himes-Ferris L, Frasier MN, McCullagh MC, Griggs JJ. Structures and processes of care in ambulatory oncology settings and nurse-reported exposure to chemotherapy. *BMJ*. 2012;21(9):753-9.