Original Article

Adverse health effects among nurses and clinical pharmacists handling antineoplastic drugs: Adherence to exposure control methods

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ABSTRACT

Background: Chronic exposure to antineoplastic drugs (ADs) may result in reproductive, liver, renal, lung, and cardiac toxicity. Moreover, bone marrow suppression, mucosal ulcers, and cancer may develop. In developing countries, adverse health effects owing to occupational exposure to ADs and adherence to safe handling guidelines are not well documented.
Aim: This study was conducted to determine the health effect of occupational exposure to ADs and evaluate adherence to control methods.
Materials and Methods: A comparative cross-sectional approach was adopted. ADs-exposed nurses and clinical pharmacists (n=54) were compared with nonexposed group (n=54). Self-reported clinical manifestations. and use of exposure controls were reported via an interview questionnaire. Blood samples were collected for complete blood count and liver and kidney function tests.
Results: Significantly higher rate of impaired fertility (31%) and oral ulcers (36.36%) were reported by ADs-exposed nurses and clinical pharmacists compared with nonexposed group (3.8 and 7.4%, respectively; *P=0.01* and *P=0.00*, respectively). Moreover, ADs-exposed group had significantly lower mean white blood cell count (6518±2064.79/µl) and significantly higher mean creatinine level (056±0.13 mg/dl) compared with nonexposed group (7307±2001.4/µl and 0.51±0.12 mg/dl, respectively; t=2.02, *P=0.04*; and *P=0.04*, respectively). Inadequate controls were reported, mainly lack of medical surveillance (100%), lack of training (69.1%), insufficient handling practices, and low usage of personal protective equipment, particularly among nurses.
Conclusion: The study highlighted chronic adverse effects associated with occupational exposure to ADs and inadequate implementation of exposure control methods. Findings necessitate raising awareness among ADs-exposed nurses and clinical pharmacists to introduce engineering controls, conduct hazard awareness training, initiate medical surveillance program, and ensure adherence to safe handling practices.

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Key Words: Adverse effects, antineoplastic agents, clinical pharmacists, hazard control, nurses.

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INTRODUCTION

Antineoplastic agents (cancer chemotherapy drugs and cytotoxic drugs) affect both neoplastic cells as well as normal cells, particularly those cells that exhibit rapid activity and growth, such as bone marrow tissue and hair follicles[1]. Clinical pharmacists who prepare these drugs or nurses who administer them to patients (and/or sometimes prepare them) are the two occupational groups who have the highest potential exposure to antineoplastic drugs (ADs)[2]. External contamination of vials by ADs residues and consequently contamination of air and surfaces in the pharmacy and administration work areas may reach more than 60%[3]. Consequently, significant amounts of harmful agents can be absorbed via unprotected skin or inhalation of the powder and liquid aerosols[4,5].

In literature, adverse health effects owing to long-term exposure to ADs in patients with cancer are well-documented[2]; however, most studies on occupational exposure to ADs have focused on environmental contamination or measurement of the exposure level[4,6–9]. Studies that examined adverse health effects owing to occupational exposure to ADs were conducted in developed countries[4,7,8,10,11]. On the contrary, few studies demonstrated the health effect in developing countries such as China[12]. In Egypt, few studies were conducted 20 years ago to evaluate genotoxicity and chromosomal aberrations owing to occupational exposure to cytotoxic drugs[13,14], and only one study was recently published[15].

Studies revealed that reproductive toxicity may

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be presented in the form of infertility (temporary or permanent), spontaneous abortions, and preterm births[16,17]. In addition, organ toxicity such as liver, renal, lung, and cardiac toxicity may develop. Moreover, bone marrow suppression, mucosal ulcers, and bleeding could occur. Exposure to ADs might also lead to hair loss and infections owing to immunological suppression and reduced white blood cell (WBC) count[12]. Additionally, there is a risk of development of cancer[18]. The International Agency for Research on Cancer in Lyon, France, currently lists 11 antineoplastic agents and two combined therapies as group 1 (human carcinogens), 12 as group 2A (probable human carcinogens), and 11 as group 2B (possible human carcinogens)[19].

Factors that may increase the risk of contamination and occupational exposure include insufficient protective conditions at workplace, incorrect operation, lack of hazard awareness, unsafe work practices, lack of adherence to the use of personal protective equipment (PPE), and long-term occupational exposure[5,6,20].

Guidelines that include specific methods for the safe handling of ADs to alleviate workplace hazards have been available for approximately three decades[2,21–23]. Several studies in developed countries evaluated ADs exposure control methods including engineering, administrative, work practices controls, and PPE usage by ADs-exposed personnel[24–29]. Yet, in developing countries, information about adherence to exposure control methods that protect ADs-exposed healthcare workers during the performance of their jobs is not well documented[12].

In Alexandria, Egypt, for a long period of time in the past years, the preparation and administration of injectable ADs in hospitals and oncology centers, have been handled by nurses in an open-plan treatment area under poorly controlled conditions. Recently in some hospitals and oncology centers, a centralized ADs preparation and admixture unit (CAPU) with better protection and safety precaution has been implemented to minimize contamination and occupational exposure to ADs. In CAPU, well-trained clinical pharmacists prepare, admix, and pack ADs inside biological safety cabinets, and then packed ADs are delivered to be administrated to patients by nurses in the treatment area. Although CAPU represents a safe way for reducing the potential occupational risk from ADs exposure[12], yet few CAPUs exit in Alexandria with few number of clinical pharmacists (Elbadry I.M., Professor of Clinical Oncology, Head of Cancer Management and Research department, Medical Research Institute; oral communication, 16 October 2016).

The potential for adverse health effects from occupational exposure to ADs has not been taken seriously by most hospital managers, clinical pharmacists, and nurses themselves. This could be attributed to lack of essential information regarding magnitude of this problem. Moreover, the implementation of exposure control methods has not been evaluated.

The current study was conducted to determine the potential adverse health effects associated with occupational exposure to ADs and assess adherence to exposure control methods.

MATERIALS AND METHODS

Study design

A comparative cross-sectional approach was adopted. ADs-exposed nurses and clinical pharmacists were compared with another group of nonexposed nurses and physicians.

Study setting

The study was conducted at oncology centers that provide both ADs preparation and ADs administration services in Alexandria city and agreed to participate in the research. Those were (a) Oncology Medicine Department at the Alexandria Faculty of Medicine, (b) Cancer Management and Research Department at the Medical Research Institute, and (c) one non-Governmental Oncology Center.

Sampling

All ADs-exposed nurses and clinical pharmacists, who were registered and practicing during the fieldwork period of the study, were invited to participate (n=72). Initially, 63 responded and had willingness to participate (87.5%). However, four nurses and two clinical pharmacists were excluded because their profession duration/occupational history was less than 2 years at the time of the study. Moreover, two supervisory nurses were excluded because they were not involved in mixing and/or administration of ADs. Those who were included in the research (n=55) represented 76.3% of the overall number of oncology nurses and clinical pharmacists. Another group of nonexposed nurses and physicians who worked at surgical, internal medicine, and cardiology departments at the University Hospitals was included (n=54). ADs-exposed group and nonexposed group were matched regarding their sex, age, marital status, and profession duration.

Study tools

All participants were subjected to the following research tools: an interview questionnaire.

A structured interview questionnaire was used to collect information regarding the following:
(a) sociodemographic data and occupational history including profession duration.
(b) self-reported adverse reproductive outcomes including impaired fertility (inability to conceive for >12 months) and history of spontaneous abortions (unintentional expulsion of an embryo or fetus before the 20th week of gestation).
(c) self-reported hair loss, where the severity of hair loss

was graded as minimal, moderate, or severe according to pull test, which entails gentle traction on a group of hairs from proximal to distal end. Hairs coming out with each pull were counted. If less than 10% of pulled hairs come out, is considered as minimal hair loss, up to 20% is moderate hair loss, and over 30% is severe hair loss[30].
(d) frequency of oral ulcers were self-reported as none, occasional (1–4/year), or frequent (≥5/year).
(e) self-reported use of engineering, administrative, and work practice control measures and PPE usage.

Collection of blood samples to evaluate organ toxicity

Blood samples were collected to conduct the following laboratory investigations:
(a) complete blood count[31] for evaluation of WBC count and differential, platelet count, RBC count, and RBC indices including hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width. For each participant, the value of each parameter was compared with reference range calculated according to age and sex; any value outside the reference range was considered as an abnormal value.
(b) Liver function tests were evaluated by measuring serum alanine transaminase (ALT) and serum aspartate transaminase (AST) levels[32]. The reference values of female were 5–33 and 5–32 U/l for ALT and AST, respectively. The reference values of male were 5–41 and 5–40 U/l for ALT and AST, respectively.
(c) Kidney function tests were evaluated by measuring the level of serum creatinine (CRE) and blood urea nitrogen (BUN)[33]. The normal ranges were 7–23.4 and 0.25–1.20 mg/dl, respectively. Any biochemical parameter outside the normal range was considered as a positive sign of organ toxicity. Blood samples were analyzed at the Central Laboratories at the Alexandria Faculty of Medicine. Data were collected from the beginning of August 2016 to the end of December 2016.

Statistical analysis of the data

The collected data were coded, typed onto computer files, tabulated, and analyzed using SPSS software program version 20 (Released 2011, IBM SPSS Statistics for Mac; IBM Corp., Armonk, New York, USA)[34]. Descriptive statistics included frequency, percentages, mean, and SD. Analytic statistics including parametric and nonparametric tests: Student's t-test and Mann–Whitney test for quantitative variables, and $\chi 2$-test, Fisher's exact test, and Monte Carlo test for qualitative variables were conducted to reveal statistically significant differences between ADs-exposed group and nonexposed group regarding self-reported clinical manifestations, and results of laboratory investigations. In addition, a comparison between ADs-exposed oncology nurses (n=37) and clinical pharmacists (n=18) regarding the use of engineering, administrative, work practice controls, and PPE usage was done. For all analyses, the level of significance was considered at 5% (α=0.05).

Ethical considerations

The study was approved by the Research Ethics Committee of Faculty of Medicine, Alexandria University. An informed written consent was obtained from each participant at the beginning of the study after explanation of the objectives of the study, procedures, and types of information to be obtained. Moreover, participants were aware that they could withdraw from the study at any time without penalty. Collected data were kept confidential.

RESULTS

The age of ADs-exposed group ranged from 19 to 57 years, with mean age of 35.47±10.68 years. Most were females (92.7%), and 56.4% were married. Most of the participants ADs-exposed group (n=55) comprised 37 (67.3%) nurses and 18 (32.7%) clinical pharmacists. Their profession duration ranged from 2 to 34 years, with mean value of 9.5±8.9 years (Table 1).

Table 1: Sociodemographic and occupational characteristics of antineoplastic drugs-exposed nurses and clinical pharmacists at oncology centers in Alexandria, 2016

Sociodemographic and occupational characteristics	Nonexposed group (n=54) [n (%)]	ADs-exposed group (n=55) [n (%)]	Test of significance (*P* value)
Sex			
Male	1 (1.9)	4 (7.3)	$^{FE}P=0.36$
Female	53 (98.1)	51 (92.7)	
Age			
Minimum–maximum	22–59	19–57	t=-0.066 (0.50)
Mean ±SD	34.0.3±11.81	35.47± 10.68	
Marital status			
Single	27 (50)	24 (43.6)	$\chi 2$=0.44 (0.50)
Married	27 (50)	31 (56.4)	

Occupation			
Nurse	34 (63)	37 (67.3)	$\chi 2$=0.22 (0.63)
Clinical pharmacist[a]/physician[b]	20 (37)	18 (32.7)	
Department			
Oncology	-	55 (100)	
Internal Medicine	17 (31.5)	-	
Surgery	14 (25.9)	-	
Cardiology	23 (42.6)	-	
Profession duration			
Minimum–maximum	2–40	2–34	$^{MW}P=0.06$
Mean±SD	13.55± 11.40	9.5±8.90	

ADs: Antineoplastic drugs, FE: Fisher's exact test, MW: Mann–Whitney test, $\chi 2$: Chi square test; t: student t-test
[a]ADs-exposed group.
[b]Nonexposed group

Clinical manifestations, as reported by both groups, are presented in Table 2. Married females in ADs-exposed group (n=29) and nonexposed group (n=26) were asked to report adverse reproductive outcomes. The rate of impaired fertility was significantly higher among ADs-exposed group (31%) compared with nonexposed group (3.8) ($^{FE}P=0.01$). On the contrary, no significant difference was found between both groups regarding number of spontaneous abortions and preterm pregnancies.

No significant difference was found regarding severity of hair loss. However, 23.6 and 12.7% of ADs-exposed group reported occasional and frequent occurrence of oral ulcers, respectively, compared with 7.4%, and 0.00% of nonexposed group, respectively; the difference was statistically significant ($^{MC}P=0.00$; Table 2).

Table 2: Self-reported adverse reproductive outcomes, hair loss, and occurrence of oral ulcers among antineoplastic drugs-exposed nurses and clinical pharmacists at oncology centers in Alexandria, 2016

Clinical manifestations	Nonexposed group [n (%)]	ADs-exposed group [n (%)]	Test of significance (*P* value)
Impaired fertility	n=26[a]	n=29[a]	
No	25 (96.2)	20 (69)	$^{FE}P=0.01$*
Yes	1 (3.8)	9 (31)	
Spontaneous abortions			
None	15 (57.7)	23 (79.3)	$^{MC}P=0.20$
<3 times	10 (38.5)	5 (17.2)	
≥3 times	1 (3.8)	1 (3.4)	
Preterm pregnancies			
None	25 (96.2)	25 (86.2)	$^{MC}P=0.49$
Once	1 (3.8)	2 (6.9)	
Twice	0 (0)	2 (6.9)	
Severity of hair loss	n=54	n=55	
Minimal (−)	24 (44.4)	15 (27.3)	$\chi 2$=4.17 (0.12)
Moderate (+)	15 (27.8)	16 (29.1)	
Sever (++)	15 (27.8)	24 (43.6)	

Occurrence of oral ulcers	n=54	n=55	
None (−)	50 (92.6)	35 (63.6)	$^{MC}P=0.00^{**}$
Occasional (+)	4 (7.4)	13 (23.6)	
Frequent (++)	0 (0)	7 (12.7)	

ADs, antineoplastic drugs, FE: Fisher's exact test, MC: Monte Carlo test, χ2: Chi square test
[a]Number of married females.
*Significant at *P≤0.05* (two-tailed).
**Significant at *P≤0.01* (two-tailed).

Complete blood count

The mean WBCs count was significantly lower among ADs-exposed group (6518±2064.79/µl) compared with nonexposed group (7307±200l.40/µl P=0.04). On the contrary, there was no statistically significant difference between both groups regarding mean RBCs count, mean platelets count, and presence of abnormalities in blood cell counts (Table 3).

Table 3: Blood cell count among antineoplastic drugs-exposed nurses and clinical pharmacists at oncology centers in Alexandria, 2016

Blood cell count	Nonexposed group (n=54)	ADs-exposed group (n=55)	Test of significance (*P* value)
RBCs count (10^6/µl)			
Minimum–maximum	4.00–5.54	3.66–5.62	*t*=−0.08 (0.93)
Mean ±SD	4.61±0.31	4.64± 0.42	
WBCs count (per µl)			
Minimum–maximum	4300–13 000	2800–12 900	*t*=2.02 (0.04)*
Mean ±SD	7307± 2001.40	6518± 2064.79	
Platelets count (per µl)			
Minimum–maximum	109 000–429 000	177 000–485 000	$^{MW}P=(0.11)$
Mean ±SD	2946.11± 59 145.6	286 333.33± 61 017.78	
Abnormalities in blood cell count			
RBCs			
Normal	45 (83.3)	47 (85.5)	$^{MC}P=0.69$
Abnormal (low)	0 (0)	1 (1.8)	
Abnormal (high)	9 (16.7)	7 (12.7)	
WBCs			
Normal	50 (92.6)	50 (90.9)	χ2=5.79 (0.05)
Abnormal (low)	0 (0)	4 (7.3)	
Abnormal (high)	4 (7.4)	1 (1.8)	
Platelets			
Normal	53 (98.1)	53 (96.4)	^{MC}P=0.49
Abnormal (low)	1 (1.9)	0 (0)	
Abnormal (high)	0 (0)	2 (3.6)	

ADs: antineoplastic drugs, MC: Monte Carlo test, MW: Mann–Whitney test, χ2: Chi square test, RBCs: red blood cells, WBCs: white blood cells.
*Significant at *P≤0.05* (2-tailed)

Moreover, the mean MCH and MCHC were significantly lower among ADs-exposed group (26.38 ± 2.79 fl and 32.08 ± 1.21 g/dl, respectively) compared with nonexposed group (27.24±2.07 fl and 32.65±0.88 g/dl, respectively) ($^{MW}P=0.03$; and t=2.77, $P=0.00$, respectively). No statistically significant difference was found between both groups regarding other RBC indices (Table 4).

Table 4: Red blood cell indices among antineoplastic drugs-exposed nurses and clinical pharmacists at oncology centers in Alexandria, 2016

RBC indices	Nonexposed group (n=54)	ADs-exposed group (n=55)	Test of significance (*P* value)
Hemoglobin (g/dl)			
Minimum–maximum	10.00–15.40	8.20–16.60	*t*=1.58 (0.11)
Mean ±SD	12.56± 1.08	12.21± 1.46	
Hematocrit (PCV) (%)			
Minimum–maximum	31.00–46.30	10.10–48.50	$^{MW}P=0.22$
Mean ±SD	38.47±3.07	37.47± 5.55	
MCV (fl)			
Minimum–maximum	64.70–97.60	59.50–92.70	*t*=1.17 (0.24)
Mean ±SD	83.43± 6.06	82.10± 6.73	
MCH (pg)			
Minimum–maximum	19.50–30.20	17.40–31.10	$^{MW}P=0.03$*
Mean ±SD	27.24± 2.07	26.38± 2.79	
MCHC (g/dl)			
Minimum–maximum	30.10–34.30	29.20–34.20	*t*=2.77(0.00)**
Mean ±SD	32.65± 0.88	32.08± 1.21	
RDW (%)			
Minimum–maximum	12.7–17.30	12.80–19.20	$^{MW}P=0.71$
Mean ±SD	14.24± 0.89	14.50± 1.31	

ADs: antineoplastic drugs, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, MCV: mean corpuscular volume, MW: Mann–Whitney test, t: student t-test, RBC: red blood cell, RDW: red cell distribution width.
*Significant at $P\leq0.05$ (two-tailed).
**Significant at $P\leq0.01$ (two-tailed).

Liver and kidney function tests

The mean CRE level was significantly higher among ADs-exposed group (0.56±0.13 mg/dl) compared with nonexposed group (0.51±0.12 mg/dl; $^{MW}P=0.04$). On the contrary, there was no statistically significant difference between both groups regarding mean ALT, AST, BUN levels, and abnormalities in liver and kidney functions (Table 5).

Table 5: Liver and kidney function tests among antineoplastic drugs-exposed nurses and clinical pharmacists at oncology centers in Alexandria, 2016

Liver and kidney FTs	Nonexposed group (n=54)	ADs-exposed group (n=55)	Test of significance (*P* value)
ALT (U/l)			
Minimum–maximum	5–63	6–44	$^{MW}P=0.71$
Mean ±SD	15.83± 11.52	14.81± 8.42	
AST (U/l)			
Minimum–maximum	11– 61	8–53	$^{MW}P=0.14$
Mean ±SD	18.90± 7.86	17.62± 7.26	

BUN (mg/dl)			
Minimum–maximum	6.50–18.70	6.50–19.20	*t* = -1.54 (0.12)
Mean ±SD	10.23± 2.55	11.07± 3.09	
CRE (mg/dl)			
Minimum–maximum	0.32–1.03		
Mean ±SD	0.51± 0.12		
Abnormalities in liver and kidney FTs			
ALT			
Normal	49 (90.7)	52 (94.5)	$^{FE}P=0.48$
Abnormal (high)	5 (9.3)	3 (5.5)	
AST			
Normal	52 (96.3)	54 (98.2)	^{FE}P=0.61
Abnormal (high)	2 (3.7)	1 (1.8)	
BUN			
Normal	53 (98.1)	54 (98.2)	^{FE}P=1
Abnormal (low)	1 (1.9)	1 (1.8)	
CRE			
Normal	54 (100)	55 (100)	-

ADs: antineoplastic drugs, FTs: function tests, ALT: serum alanine transaminase, AST: serum aspartate transaminase, BUN: blood urea nitrogen, CRE: serum creatinine, MW: Mann–Whitney test; FE, Fisher's exact test, t: student t-test
*Significant at $P \leq 0.05$ (two-tailed).

Self-reported use of engineering, administrative, work practice controls, and personal protective equipment by antineoplastic drugs-exposed nurses and clinical pharmacists

Exposure control methods, as reported by the ADs-exposed group, are demonstrated in Table 6. Clinical pharmacists were responsible for preparation and constitution of ADs at CAPUs. On the contrary, 13 nurses have been preparing and reconstituting ADs at open-plan treatment areas, and 24 nurses were responsible for administration of ADs to the patients. Biological safety cabinets and ventilation devices were implemented at CAPUs; one biological safety cabinet is present in each unit. Moreover, significantly lower percentage of nurses reported receiving hazard awareness training or ADs safe handling training courses (13.5%) compared with the clinical pharmacists (66.7%) ($\chi2$=16.02, *P=0.00*). All ADs-exposed group reported lack of medical surveillance program at their workplace.

Regarding adequate safe handling practices, significantly higher percentage of clinical pharmacists (38.9%) reported storage and transportation of the final product sealed in transport bags compared with nurses (8.1%) ($^{FE}P=0.01$). Significantly higher percentage of clinical pharmacists (72.2%) reported safe disposal of used materials in appropriate containers compared with nurses (8.1%) ($\chi2$=24.13, *P=0.00*), and significantly higher percentage of clinical pharmacists (83.3%) reported appropriate management of drug spills according to written policies compared with nurses (18.9%) ($\chi2$=20.93, *P=0.00*). Furthermore, all clinical pharmacists reported wearing single gloves compared with 67.6% of nurses; besides, most clinical pharmacists reported wearing gowns and surgical masks (94.4 and 72.2%, respectively) compared with nurses (8.1 and 8.1%, respectively). The difference between them regarding usage of gloves, gowns, and masks was statistically significant ($^{FE}P=0.00$; $\chi2$=39, *P=0.00*; and $\chi2$=24.13, *P=0.00*, respectively; Table 6).

Table 6: Self-reported use of engineering, administrative, work practice controls, and personal protective equipment by antineoplastic drugs-exposed oncology nurses and clinical pharmacists at oncology centers in Alexandria 2016

Self-reported control methods	Oncology nurses (n=37) [n (%)]	Clinical pharmacists (n=18) [n (%)]	Test of significance (*P value*)
Role at oncology department			
Preparation and reconstitution of ADs	13 (35.1)	18 (100)	$\chi2$=20.71 (0.00)**
Administration of ADs to patients	24 (64.9)	0 (0)	
Engineering control measures at workplace			
Ventilation device	0 (0)	18 (100)	FEP=0.00**
Biological safety cabinets	0 (0)	18 (100)	$\chi2$=55 (0.00)**
Administration control measures			
Received safety training for adherence to a standard protocol	5 (13.5)	12 (66.7)	$\chi2$=16.02 (0.00)**
Medical surveillance program exists at workplace	0 (0)	0 (0)	
Safe handling practices			
Store/transport final product sealed in transport bags	3 (8.1)	7 (38.9)	FE*P=0.01**
Dispose used materials in appropriate containers	3 (8.1)	13 (72.2)	$\chi2$=24.13 (0.00)**
Manage spills according to written policies and procedures	7 (18.9)	15 (83.3)	$\chi2$=20.93 (0.00)**
Use of PPE			
Gloves	25 (67.6)	18 (100)	FE*P=0.00***
Gowns	3 (8.1)	17 (94.4)	$\chi2$=39 (0.00) **
Masks	3 (8.1)	13 (72.2)	$\chi2$=24.13 (0.00)**

ADs, antineoplastic drugs, FE: Fisher's exact test, $\chi2$: Chi square test, PPE: personal protective equipment.
*Significant at *P≤0.05* (two-tailed).
**Significant at *P≤0.01*(two-tailed).

DISCUSSION

In the present study, ADs-exposed nurses and clinical pharmacists reported significantly higher rate of impaired fertility and oral ulcers. Similarly, Zhang *et al.*[12], in China, reported that nurses exposed to ADs experience more difficulties in conceiving and have more frequent oral ulcers than nonexposed nurses. In addition, other studies[9,17] revealed that long-term ADs exposure may lead to infertility, and it increases liability to infections.

Regarding hematological parameters in the present study, the mean WBC count, a biomarker for ADs hazard[12], was significantly lower among ADs-exposed nurses and clinical pharmacists compared with nonexposed group. This indicates immune suppression and explains the significantly higher rate of oral ulcers among ADs-exposed group. This finding coincides with the result of Zhang *et al.*[12], in China, where the mean WBC was significantly lower in oncology nurses than in nonexposed nurses. His study also revealed significantly higher number of oncology nurses with abnormal WBC count compared with nonexposed nurses. However, in the current study, there was no significant difference regarding abnormalities in blood cell counts. This could be attributed to a relatively smaller sample size in the present study. Immunological suppression and reduced WBC count owing to ADs exposure were also reported in another study[2].

Regarding RBC indices, few studies examined the association between exposure to ADs and changes in RBCs indices and were conducted among patients with cancer receiving ADs[35,36]. Wenzel *et al.*[35], showed that exposure to certain ADs may lead to an increase in MCV. Moreover, the European Cancer Anemia Survey[36] reported that ~83% of patients receiving ADs developed chemotherapy-induced anemia, a hemoglobin level less than 12.0 g/dl. In the present study, although no significant difference in hemoglobin level or MCV was found between both groups, yet, significantly lower mean MCH and MCHC were reported in the ADs-exposed group compared with nonexposed group. In practice, the values of MCH and MCHC are used to explain the etiology of anemias; MCH quantifies the amount of hemoglobin per red blood cell, whereas MCHC correlates the hemoglobin content with the volume of the cell[37]. In literature, chemotherapy-induced anemia is well documented[38]; however, whether ADs exposure has an effect on MCH or MCHC levels is not well documented.

Regarding liver and kidney toxicity, in the current

study, the mean CRE level was significantly higher in ADs-exposed group compared with nonexposed group, yet, no significant difference between both groups was found on studying abnormalities in ALT, AST, BUN, and CRE levels. On the contrary, Zhang *et al.*[12], in China, reported significantly higher incidence of abnormal liver and kidney functions among oncology nurses compared with nonexposed nurses. Similarly, liver and kidney toxicities were reported in another study[2]. The varied results could be attributed to difference between studies regarding sample size, profession duration, and sufficiency of workplace control procedures as well as PPE usage. Besides, kidney and liver damage might be influenced by other factors, for example, age, preexisting medical condition such as diabetes or elevated blood pressure, family history of kidney or liver disease, reduced fluid intake, and other dietary factors[39,40].

ADs elimination or substitution by a less toxic substance is not feasible, thus, guidelines specify the following exposure control methods:
(a) engineering controls including biological safety cabinets and closed-system transfer devices.
(b) administrative controls such as hazard awareness training, and medical surveillance.
(c) work practice controls such as cleaning spilled chemicals immediately according to written policies.
(d) PPE usage of mainly chemotherapy-tested gloves, single-use disposable gowns, respirators/masks, and eye protection[25].

In the present study, biological safety cabinets and ventilation device were implemented only at CAPUs, whereas most ADs-exposed group participants (67.2%) have been preparing ADs in an open-plan treatment area. Only one-third of ADs-exposed group participants have received, before or on-job, specialized training courses to become aware about the hazard and understand safe handling practices. Additionally, all ADs-exposed nurses and clinical pharmacists reported lack of medical surveillance program at their workplace; none of them have conducted medical monitoring. In addition, low percentage adopted safe handling practices at their workplace such as transport of the final product sealed in transport bags, safe disposal, and appropriate management of drug spills (18.2, 29.1, and 40%, respectively). Furthermore, most reported wearing single gloves (78.2%), whereas only 36.4 and 29.1% reported wearing gowns and surgical masks, respectively. In the current study, although significantly higher percentage of clinical pharmacists were adherent to safe handling guidelines compared with nurses, yet, the overall implementation of exposure control measures was inadequate.

The results of the current study coincides with findings of other studies conducted to evaluate adherence to precautionary guidelines for handling ADs, for example, in the study by Boiano *et al.*[25], similar precautionary guidelines were deficient; however, the performance of nurses versus clinical pharmacists was different. Nurses in their study had better performance in certain guidelines and low performance in others compared with pharmacy practitioners. On the contrary, nurses in the current study reported low performance/adherence to all control methods compared with clinical pharmacists[25]. Another study showed that oncology nurses use gloves, but gown use remains comparatively low[28]. Furthermore, a survey conducted on a sample Massachusetts nursing population revealed that only 6% of nurses had training on safe handling procedures, 56% indicated no special engineering controls at their workplace, and none was aware of the National Institute for Occupational Safety and Health recommended exposure assessment strategies[29].

LIMITATIONS OF STUDY

Participation in the current study was completely voluntary. Although response rate was 87.5%, yet, the sample size was relatively small. This is attributed to low overall number of registered oncology nurses and clinical pharmacists at the two oncology departments and the oncology center despite that those are the largest three oncology treatment centers in Alexandria City. The current cross-sectional design revealed possible association between occupational exposure to ADs and adverse outcomes; however, prospective studies are better to examine exposure-effect relationship and avoid recall bias. Moreover, it would be better to consider certain factors such as having diabetes or elevated blood pressure, family history of kidney or liver disease, and dietary factors in the current study, as those factors might influence the results of liver and kidney function tests.

CONCLUSION

This study highlighted chronic adverse health effects associated with occupational exposure to ADs namely impaired fertility, suppressed immunity manifested by oral ulcers and reduced mean WBCs count, and increased mean CRE level. Moreover, the study revealed inadequate implementation of exposure controls particularly among nurses.

It is recommended to utilize the study findings to raise awareness of ADs-exposed personnel regarding ADs hazards and the importance of PPE usage. Additionally, it is recommended to raise awareness among employers to introduce engineering controls in a large scale, conduct hazard awareness training courses, initiate medical surveillance program, and ensure adherence to safe handling practices. In addition, large cross-sectional surveys on ADs-exposed personnel in developing countries are recommended, and occupational exposure to ADs has

to be evaluated in future research.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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