Association between Occupational Exposure and Control Measures for Antineoplastic Drugs in a Pharmacy of a Hospital

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Objectives: To investigate the association between occupational contamination and exposure levels to antineoplastic drugs and the application of control measures in a hospital work environment.

Methods: Wipe samples of equipments were collected at a hospital in Osaka Prefecture, Japan, from 2007 to 2011. These samples were subjected to measurements of cyclophosphamide (CP), gemcitabine (GEM), platinum-containing drugs (Pt), and fluorouracil (5FU). Additionally, 24-h urine samples were collected from pharmacists who handled antineoplastic drugs, which were analyzed for CP and alpha-fluoro-beta-alanine (AFBA). The application of control measures was scored according to a checklist, which consisted of the following five items: safety equipment and maintenance, training and documentation, devices for safe handling, personal protective equipment, and emergency care. The aim was to obtain a score of 80%.

Results: The median CP, GEM, and 5FU concentrations of all wipe samples were significantly lower during the period when the mean score was >80% (attainment period) versus when the mean score was ≤80% (nonattainment period; all \( P < 0.001 \), Mann–Whitney’s \( U \)-test). Additionally, the median urinary CP and AFBA concentrations of pharmacists during the attainment period tended to be lower than that of those during the nonattainment period (\( P = 0.061 \) and 0.061, respectively, using Mann–Whitney’s \( U \)-test).

Conclusions: Contamination and levels of exposure to antineoplastic drugs decreased with a score higher than 80%. The scores of the items on the checklist appeared to adequately reflect the condition of the control measures, as increases in all five items were associated with reductions in the contamination by and levels of exposure to all drugs.

Keywords: antineoplastic drugs; biological monitoring; checklist; pharmacy; surface contamination

INTRODUCTION

Antineoplastic drugs are required for the treatment of cancer. However, there are concerns regarding
the health risks they may pose to healthcare workers who handle these drugs (Shirato, 1992; Tomioka and Kumagai, 2005; Connor and McDiarmid, 2006). The US National Institute for Occupational Safety and Health (NIOSH) reported that occupational exposure to hazardous drugs, including antineoplastic drugs, may increase skin rashes, infertility, miscarriage, genotoxic damage, and leukemias or other cancers (NIOSH, 2004). In 2007, guidelines for the safe handling of antineoplastic drugs were formulated by the International Society of Oncology Pharmacy Practitioners Standards Committee (ISOPP, 2007). In Japan, guidelines for handling antineoplastic drugs in hospitals were issued by the Japanese Pharmaceutical Association in 1991, and these were later revised in 2005 and 2009 (Kitada et al., 2005, 2009). Tests, such as genotoxicity testing, as well as measurement of levels of antineoplastic drugs on wipe samples of equipment and urine samples of healthcare workers, have been previously implemented to identify the occupational risk factors of antineoplastic drugs (Hedmer et al., 2008; Connor et al., 2010). In Japan, nurses have been exposed to these drugs and it has been suggested that lymphocyte DNA damage could have been induced by such drugs (Yoshida et al., 2006; Sasaki et al., 2008). Furthermore, antineoplastic drugs have been previously detected in wipe samples of equipment found in the preparation room, as well as in urine samples of healthcare workers who did and did not handle antineoplastic drugs (Sugiura et al., 2011a, 2011b; Yoshida et al., 2011a).

To prevent exposure to antineoplastic drugs, the guidelines also recommend that healthcare workers wear personal protective equipment and handle drugs in a biological safety cabinet (BSC) located in a separate room used just for the handling of antineoplastic drugs (NIOSH, 2004; ISOPP, 2007; Kitada et al., 2009). Several reports have previously shown that a closed-system device can prevent both the contamination of work environments and occupational exposure (Sessink and Ryden, 1999; Vandenbroucke and Robays, 2001; Connor et al., 2002; Nygren et al., 2002; Spivey and Connor, 2003; Wick et al., 2003; Harrison et al., 2006; Yoshida et al., 2009; Sessink et al., 2011). Indeed, in a previous study, we showed that the contamination levels of antineoplastic drugs were related to the amounts of drugs handled, the cleaning methods used on the equipment, the skill levels of the workers in maintaining negative pressure inside a vial, and the use of BSCs and closed-system devices (Yoshida et al., 2011a).

Several reports have evaluated the use of only one type of control measure, such as a closed-system device, in the workplace environment (Vandenbroucke and Robays, 2001; Connor et al., 2002; Sessink et al., 2011). Reports that comprehensively evaluate several control measures, including safety equipment, manuals, training, safety devices, and emergency response protocols, are rare. Thus, the aim of the present study was to comprehensively evaluate the availability of various control measures at a hospital in Japan. We monitored the work environment and levels of exposure to antineoplastic drugs of pharmacists at a hospital (Hospital A) in the Osaka Prefecture, Japan, between 2007 and 2011. The levels of contamination with cyclophosphamide (CP), gemcitabine (GEM), platinum-containing drugs (Pt), such as cisplatin, carboplatin, oxaliplatin, and nedaplatin, and fluorouracil (5FU) in the work environment were evaluated by wipe tests. The exposure levels of pharmacists were evaluated by the amounts of CP and alpha-fluoroo-beta-alanine (AFBA), a major metabolite of 5FU (Sessink et al., 1994; Rubino et al., 2006; Ndaw et al., 2010), in 1-day urine samples. The control measures used to handle antineoplastic drugs at Hospital A were then scored using a checklist (supplementary data are available at Annals of Occupational Hygiene online; Yoshida et al., 2011b). Lastly, we investigated the associations between the contamination with and exposure levels to antineoplastic drugs and the application of control measures at Hospital A; we also evaluated the availability of control measures for antineoplastic drugs.

METHODS

Study design

The present study was approved by the ethics review board of the Osaka Prefectural Institute of Public Health. We requested cooperation from Hospital A, where pharmacists continually prepare antineoplastic drugs, and consent was obtained. At this hospital, one to five pharmacists prepare antineoplastic drugs from Monday to Friday, between 9:00 and 17:00 h. We evaluated the preparation rooms and interviewed the pharmacists. To quantify the application of control measures, we created a checklist that assesses the safe handling of antineoplastic drugs (supplementary data are available at Annals of Occupational Hygiene online; Yoshida et al., 2011b). This checklist covered the following five items: safety equipment and maintenance, training and documentation, devices for safe handling, personal protective equipment, and emergency care. The aim was to obtain a score of at least 80%. We have two reasons why we set the score (1–8 points) for each question and decided on the score (80%) as
we did. The first reason was that we expected that a score of 80% would indicate control measures that reduced exposure to antineoplastic drugs. The second reason was it would help pharmacists understand the priorities of control measures. The pharmacists were asked to answer the questions on the checklist and the score was calculated. We also collected (i) wipe samples from equipment surfaces in the preparation rooms and (ii) 24-h urine samples from the pharmacists in October 2007, February 2008, December 2008, February 2011, and June 2011. CP, GEM, Pt, and 5FU were the selected contamination markers due to their toxicity, amount of use, and the results obtained in our previous studies (Mochizuki et al., 2008; Yoshida et al., 2008). The levels of CP, GEM, Pt, and 5FU in the wipe samples, as well as CP and AFBA in the urine samples, were measured. The relationships between the contamination levels of the antineoplastic drugs with the handling procedures for these drugs and the control measures of Hospital A were determined.

Improvement of working conditions in Hospital A

In Hospital A, pharmacists prepared antineoplastic drugs in BSC class IIA1 in the preparation room from 2004. BSC class IIA1 means approximately 70% of the air was recirculated and 30% of the air was exhausted to the preparation room. Consequently, Hospital A introduced a closed-system device (PhaSeal®, Carmel Pharma Japan, Tokyo, Japan) for the preparation of CP in January 2008. Then, in April 2008, Hospital A changed from a class IIA1 to a IIA2 BSC, instituted an antineoplastic-drug-handling manual, introduced a disposable sterilized sheet, and changed from latex to nitrile gloves (Purple nitrile extra®, Kimberly-Clark Health Care, Kanagawa, Japan). Disposable sterilized sheets were laid on the working surface of BSC in order to absorb the leaked antineoplastic drugs. BSC class IIA2 means approximately 70% of the air was recirculated and 30% air was replaced with fresh air. In 2010, Hospital A revised their antineoplastic-handling manual. The items added in their handling manual were as follows: the preparation method of closed-system device, the cleaning method of vials and ampoules before preparation, the cleaning method for BSC, the working table after preparation, and treatment method when antineoplastic drugs spread by accident.

Wipe sampling of the equipment

Wipe samples of the equipment were collected from the preparation room after all drug preparations for the day had been completed and the pharmacists had gone out of the room. The sampled surfaces included the working surfaces of the BSC (\(n = 20, 4171–5850\,\text{cm}^2\)), the front side of the air grilles of the BSC (\(n = 20, 1950\,\text{cm}^2\)), working tables (\(n = 23, 1575–3600\,\text{cm}^2\)), and floors (\(n = 25, 2500\,\text{cm}^2\)). Colored vinyl tape was put on the surfaces before each sampling occasion. Each sampling location was measured with a tape measure to determine the sampling area. We calculated nonflat surface areas, such as the front side of the air grille of the BSC, from the vertical and horizontal distance measurements obtained with a tape measure. The wipe sampling procedure was conducted according to the procedures of Sessink et al. (Sessink et al., 1992a, Yoshida et al., 2009, 2011a). Briefly, 10 ml of 0.03 M sodium hydroxide, which acted as the sampling solution, were poured onto the surface and wiped with two sheets of tissue paper (JK wiper, 150-S, 225 × 215 mm, Nippon Paper Crecia, Tokyo, Japan). Then, 20 ml of 0.03 M sodium hydroxide were added to the wipe samples, and the samples were sonicated for 1 h in an ultrasonic bath. The sample solution was extracted from the tissue by the micropipette and stored at −40°C until further use.

Urine sampling

Twenty-four-hour urine samples were collected from pharmacists who handled antineoplastic drugs at the same time as when the wipe samples were collected. The urine samples were collected from Pharmacists A and C in October 2007; Pharmacists A, D, E, and F in February 2008; Pharmacists A, D, H, I, and J in December 2008; Pharmacists L, N, and R in February 2011; and Pharmacists N, R, and S in June 2011. All urine samples were collected separately in 500-ml polypropylene wide-mouthed containers (ASONE, Tokyo, Japan) before antineoplastic drug preparation and on the next day (i.e. after 24h). The urine volume of each sample was measured, and samples were stored at −40°C until further use.

Determination of CP

CP amounts in wipe and urine samples were measured according to the procedures of Sessink et al. and other researchers (Sessink et al., 1993, Yoshida et al., 2009, 2011a). Briefly, after adding cyclophosphamide-d6 (Chemie plus Service, Aachen, Germany) and tris-hydrochloric acid buffer (1.0 M, pH 8.0) to a 5-ml sample solution, the sample was extracted twice with diethyl ether. Once evaporated, the ether extract was reacted with trifluoroacetic acid anhydride in ethyl acetate at 70°C.
for 30 min. The reacted mixture was then dried under a flow of nitrogen and reconstituted in toluene. The amounts of CP in the wipe samples were measured with a gas chromatograph (HP 5890 SERIES 2 Plus, Hewlett-Packard, Santa Clara, CA, USA) and quadrupole mass spectrometer (HP 5972, Hewlett-Packard) equipped with a DB-5MS capillary column (0.25-mm internal diameter × 30 m; 0.25-μm film thickness; Agilent, Santa Clara, CA, USA). The flow rate was 1.0 ml/min, the column temperature was 40°C, and the injection volume was 20 μl. The mean recovery rates (pH 6.5) and methanol (97 : 3, v/v). The mean recovery rates of CP from the wipe and urine samples were 92 ± 2.2% (n = 5) and 101 ± 3.3% (n = 5), respectively. The LODs of CP from the wipe and urine samples were 1.0 ng and 0.003 ng/ml, respectively. The limits of quantitation (LOQs) of CP from the wipe and urine samples were 6.0 ng and 0.02 ng/ml, respectively.

**Determination of 5FU and GEM**

The methodology for assessing 5FU and GEM amounts in wipe samples has been previously described in detail by Yoshida et al. (Yoshida et al., 2011a). Briefly, acetic acid was added to 10 ml of wipe sample and the pH was adjusted to 5.0. The sample solution was then concentrated to 2.0 ml with a centrifugal concentrator (CC-101, TOMY SEIKO, Tokyo, Japan). Internal standard was not used in this method. 5FU and GEM were measured with a high-performance liquid chromatography and ultraviolet spectrophotometer (270 nm; L-2000 Series, Hitachi High-Technologies Corporation, Tokyo, Japan) equipped with an ODS-3 packed column (4.6-mm internal diameter × 250 mm; 5.0-μm particle size; GL Science, Tokyo, Japan). The eluent was a mixture of 100 mM ammonium acetate and GEM were measured with a high-performance liquid chromatograph (HP 6890, Hewlett-Packard) and high-resolution mass spectrometer (JMS 700D, JEOL, Tokyo, Japan) equipped with a DB-5MS capillary column (0.25-mm internal diameter × 30 m; 0.25-μm film thickness; Agilent). The limits of detection (LODs) of CP from the wipe and urine samples were 1.0 ng and 0.003 ng/ml, respectively. The limits of quantitation (LOQs) of CP from the wipe and urine samples were 6.0 ng and 0.02 ng/ml, respectively.

**Determination of Pt**

The methodology for determining Pt amounts in wipe samples has been previously described in detail by Yoshida et al. (Yoshida et al., 2011a). Briefly, 1.0 ml of the sample solution was diluted with 20 ml of 1% nitric acid and then filtered through a polytetrafluoroethylene filter (DISMIC-25HP; Toyo Roshi Kaisha, Tokyo, Japan). Pt amounts were measured with an inductively coupled plasma mass spectrometer (ICPM8500, Shimadzu Corporation, Kyoto, Japan). The standards and samples were spiked with 50 μg/l iridium, which served as an internal standard. The levels of the platinum isotope (194Pt) and internal standard (193Ir) were measured. The mean recovery rate of 300 ng Pt from the wipe samples was 98 ± 15% (n = 5). The LOD and LOQ of Pt from the wipe sample were 2.0 and 10 ng, respectively.

**Determination of AFBA**

AFBA levels in urine samples were measured based on the procedures of Rubino et al. (Rubino et al., 2006). An internal standard (10 ng AFBA-13C3; Toronto Research Chemicals, Ontario, Canada) and 0.1 ml of 5 M sodium hydroxide were added to 1.0 ml of the urine sample. After adding 0.15 ml of S-ethyl-trifluoro-thio-acetate (Tokyo Chemical Industry, Tokyo, Japan), the sample was mixed overnight in a draft chamber. The reaction was then stopped with the addition of 0.1 ml of 12 M hydrochloric acid, and the sample was extracted twice with 3.0 ml ethyl acetate. The ethyl acetate extract was then dried under a flow of nitrogen and reacted with 0.5 ml of acetyl chloride/n-butyl alcohol (5 : 95, v/v) at 80°C for 60 min. Again, after being dried under a flow of nitrogen, the reacted mixture was dissolved in 1.0 ml of acetone/hexane (40 : 60, v/v). A Sep-Pak florisil cartridge (Nihon Waters, Tokyo, Japan) was conditioned with acetone and hexane, and the sample solution was loaded into the cartridge. The loaded sample solution was then followed by 5.0 ml of acetone/hexane (40 : 60, v/v), which was collected in the same vial. The sample extract was dried under a flow of nitrogen and reconstituted with 0.2 ml of acetonitrile. AFBA was then measured with a gas chromatograph and high-resolution mass spectrometer equipped with a DB-17MS capillary column (0.25-mm internal diameter × 30 m; 0.25-μm film thickness; Agilent). The gas chromatograph conditions were as follows: (i) the carrier gas was helium, and its flow rate was 1 ml/min; (ii) the injection mode was splitless (2 min); (iii) the injection volume was 1 μl; and (iv) the injection temperature was 250°C. The oven temperature was set to 100°C for 2 min; raised in increments by 40°C/min until 150°C, 5°C/min until 180°C, and 40°C/min until 280°C; and finally maintained constant at 280°C for 5 min. The high-resolution mass spectrometry conditions were as follows: (i) the resolution was 10 000; (ii) the ion-detection mode selected was ion-monitoring mode; and (iii) the ionizing mode
was set to the electronic impact-ionizing mode. The ionizing temperature was 280°C, ionizing energy was 38 eV, and ionizing current was 600 μA. The quantity ions (m/z) of AFBA and AFBA\textsuperscript{13C3} were 204.0284 and 189.0178, respectively. The mean recovery rates of 0.8 and 0.2 ng of AFBA from a 1.0-ml urine sample were 81.1 ± 11.7% (n = 5) and 81.0 ± 13.3% (n = 5), respectively. The LOD and LOQ of AFBA from urine samples were 0.016 and 0.04 ng/ml, respectively.

**Statistical analysis**

The mean score was calculated from the scores of the following checklist items: safety equipment and maintenance, training and documentation, devices for safe handling, personal protective equipment, and emergency care. The aim was to obtain a score of 80%, and consequently, the data were categorized into two periods—the nonattainment and attainment periods. The nonattainment period corresponded to a mean score ≤80%, whereas the attainment period corresponded to a mean score >80%. October 2007, February 2008, and December 2008 belonged to the nonattainment period. February and June 2011 belonged to the attainment period. Comparisons of CP, GEM, Pt, and 5FU concentrations of wipe samples between the two periods were accomplished via the Mann-Whitney’s U-test, as the data were not normally distributed. Differences in urinary concentrations of CP and AFBA of pharmacists were also determined via the Mann-Whitney’s U-test. For concentrations below the LOD, we used a value equal to the LOD divided by the square root of two (Hornung and Reed, 1990). Statistical analyses were conducted with PASW Statistics 18 software (SPSS Japan, Tokyo, Japan). A value of $P < 0.05$ was considered statistically significant.

**RESULTS**

The characteristics and amounts of CP, GEM, Pt, and 5FU obtained from the preparation room are presented in Table 1. Of the drugs available at the hospital, 5FU was stored only in one volume size and was available in the ampoule form. The mean amounts of CP, GEM, Pt, and 5FU handled were 3500, 27 600, 2040, and 23 600 mg/day, respectively. The median amounts of CP, GEM, Pt, and 5FU handled were 3500, 24 000, 2200 and 22 000 mg/day, respectively. The checklist scores and the number of pharmacists of Hospital A are presented in Fig. 1. The mean degrees of attainment in October 2007, February 2008, December 2008, February 2011, and June 2011 were 37.4, 41.4, 66.8, 80.6, and 80.6%, respectively. The wipe test results of the equipments in Hospital A are presented in Table 2. During the nonattainment period (from 2007 until 2010), CP, GEM, Pt, and 5FU were detected in 83, 85, 79, and 81% of all wipe samples, respectively. During the attainment period, CP, GEM, Pt, and 5FU were detected in 44, 11, 31, and 17% of all wipe samples, respectively. During the attainment period, CP, GEM, Pt, and 5FU were detected in 83, 85, 79, and 81% of all wipe samples, respectively. During the attainment period, CP, GEM, Pt, and 5FU were detected in 44, 11, 31, and 17% of all wipe samples, respectively. During the attainment period, CP, GEM, and 5FU concentrations of all wipe samples were significantly lower for all sampled locations during the attainment period compared with the same in the nonattainment period. Moreover, the median Pt concentrations of wipe samples from the working surface of the BSC, front side of the air grille of the BSC, and the working table were also significantly lower during the attainment period compared with the values in the nonattainment period.

The CP and AFBA amounts found in the urine samples of pharmacists who handled antineoplastic drugs in Hospital A are presented in Fig. 2. During the nonattainment period, urinary CP and AFBA were detected in 45% (5/11) and 55% (6/11) of the pharmacists, respectively. During the attainment period, urinary CP and AFBA were detected in 89% (9/10) and 91% (9/10) of the pharmacists, respectively.

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**Table 1. Characteristics and amounts (mg/day) of cyclophosphamide (CP), gemcitabine (GEM), platinum-containing drugs (Pt), and fluorouracil (5FU) prepared in the preparation room of Hospital A.**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Formulation of drug</th>
<th>Volume</th>
<th>Container type</th>
<th>Amount (mg/day) Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>Powder</td>
<td>100, 500 mg</td>
<td>Vial</td>
<td>3700</td>
<td>2800</td>
</tr>
<tr>
<td>GEM</td>
<td>Powder</td>
<td>200, 1000 mg</td>
<td>Vial</td>
<td>24 000</td>
<td>22 000</td>
</tr>
<tr>
<td>Pt</td>
<td>Powder and liquid</td>
<td>10, 50, 100, 150, 450 mg; 10 mg/20 ml, 25 mg/50 ml, 50 mg/100 ml, 50 mg/10 ml, 100 mg/20 ml</td>
<td>Vial</td>
<td>1300</td>
<td>1100</td>
</tr>
<tr>
<td>5FU</td>
<td>Liquid</td>
<td>250 mg/5 ml</td>
<td>Ampoule</td>
<td>21 000</td>
<td>22 000</td>
</tr>
</tbody>
</table>

* Cisplatin, carboplatin, oxaliplatin, and nedaplatin were present in Hospital A.
period, urinary CP and AFBA were detected in 0% (0/6) and 17% (1/6) of the pharmacists, respectively. The median urinary CP and AFBA concentrations of the pharmacists tended to be lower in the attainment versus nonattainment period; however, they were not significant (P = 0.061 and 0.061, respectively).

DISCUSSION

The association between control measures, as determined from the scores on the checklist used, and occupational exposure levels to antineoplastic drugs at Hospital A between 2007 and 2011 were investigated in the present study.

It was found that GEM and 5FU amounts were 4- to 10-fold greater than those of CP and Pt (Table 1). In a previous study, we reported that the amount of drugs handled influenced the contamination levels of the work environment (Yoshida et al., 2011a). Corroborating our previous findings, in the present study, we found that during the nonattainment period (i.e. when a mean score was ≤80%), the concentrations of GEM and 5FU were much higher than those of CP and Pt in the wipe samples collected from all sampling points. Moreover, given that the amount of drugs handled was similar throughout the study period, the change in contamination levels appeared to be dependent on the changes in the work environment, such as changing the type of BSC, revising the manual, and installing a closed-system device.

During the nonattainment period, CP, GEM, Pt, and 5FU were detected in 83, 85, 79, and 81% of all wipe samples, respectively. These results demonstrate that the entire preparation room was contaminated with antineoplastic drugs, and thus, pharmacists were being exposed to antineoplastic drugs and their associated risks, even if they did not handle any drugs. In fact, at Hospital A, some pharmacists who aided in the drug-mixing operations would enter the preparation room without wearing personal protective equipment. During the nonattainment period, the median concentrations of GEM, Pt, and 5FU on the wipe samples from the front side of the air grille were higher than those at the other sampling points. One explanation for this may be that the front side of the air grille was concentrating the air.
from the inside of the BSC and, thereby, contamination was also concentrated. Another reason may be that the front side of the air grille was difficult to clean properly.

During the attainment period (i.e. when a mean score was >80%), the median concentrations of CP, GEM, Pt and 5FU of all wipe samples decreased significantly. This finding suggests that an increased score above 80% accompanied a decrease in the contamination levels of CP, GEM, Pt and 5FU. In our previous study, the contamination levels of 5FU at Japanese hospitals were higher than those of hospitals in Europe and USA (Yoshida et al., 2011a).

One reason for this discrepancy may be that 5FU was only provided in the ampoule form in Japan. Thus, when pharmacists cut the ampoule, 5FU may spill and spread all over the disposable sterilized sheet.

Table 3 shows that the contamination levels of 5FU during the nonattainment period were higher than those reported in previous studies, wherein pharmacists prepared 5FU from a vial (Sessink et al., 1992b; Connor et al., 1999; Vandenbroucke and Robays, 2001; Sessink et al., 2011). Fortunately, this problem was addressed by revising the antineoplastic-drug-handling manual, providing additional training for the pharmacists, and ensuring that the mean score

Table 2. Concentrations (ng/cm²) of cyclophosphamide (CP), gemcitabine (GEM), platinum-containing drugs (Pt), and fluorouracil (5FU) of wipe samples from the working surface of the BSC, the front side of the air grille of the BSC, the working table, and the floor in Hospital A.

<table>
<thead>
<tr>
<th>Wipe sampling point</th>
<th>Test drug</th>
<th>Non attainment periodb</th>
<th>Attainment periodc</th>
<th>P valuee</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>Mean</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Working surface of BSC</td>
<td>CP</td>
<td>1.5</td>
<td>0.010</td>
<td>&lt;0.00017–16</td>
</tr>
<tr>
<td></td>
<td>GEM</td>
<td>36</td>
<td>4.1</td>
<td>0.81–370</td>
</tr>
<tr>
<td></td>
<td>Pt</td>
<td>0.08</td>
<td>0.005</td>
<td>&lt;0.0034–0.55</td>
</tr>
<tr>
<td></td>
<td>5FU</td>
<td>6.3</td>
<td>3.3</td>
<td>0.31–41</td>
</tr>
<tr>
<td>Front side of air grille of BSC</td>
<td>CP</td>
<td>0.98</td>
<td>0.042</td>
<td>&lt;0.00051–8.43</td>
</tr>
<tr>
<td></td>
<td>GEM</td>
<td>46</td>
<td>12</td>
<td>5.8–270</td>
</tr>
<tr>
<td></td>
<td>Pt</td>
<td>0.19</td>
<td>0.056</td>
<td>0.0029–1.4</td>
</tr>
<tr>
<td></td>
<td>5FU</td>
<td>21</td>
<td>9.4</td>
<td>&lt;0.15–98</td>
</tr>
<tr>
<td>Working table</td>
<td>CP</td>
<td>0.28</td>
<td>0.022</td>
<td>&lt;0.00026–2.37</td>
</tr>
<tr>
<td></td>
<td>GEM</td>
<td>10</td>
<td>1.8</td>
<td>&lt;0.078–99</td>
</tr>
<tr>
<td></td>
<td>Pt</td>
<td>0.24</td>
<td>0.037</td>
<td>&lt;0.0013–2.4</td>
</tr>
<tr>
<td></td>
<td>5FU</td>
<td>14</td>
<td>2.7</td>
<td>&lt;0.078–70</td>
</tr>
<tr>
<td>Floor</td>
<td>CP</td>
<td>0.19</td>
<td>0.050</td>
<td>&lt;0.00040–1.13</td>
</tr>
<tr>
<td></td>
<td>GEM</td>
<td>1.2</td>
<td>1.2</td>
<td>&lt;0.12–6.4</td>
</tr>
<tr>
<td></td>
<td>Pt</td>
<td>1.70</td>
<td>1.038</td>
<td>0.00080–0.012</td>
</tr>
<tr>
<td></td>
<td>5FU</td>
<td>0.57</td>
<td>0.50</td>
<td>&lt;0.12–1.4</td>
</tr>
<tr>
<td>Total</td>
<td>CP</td>
<td>0.70</td>
<td>0.037</td>
<td>&lt;0.00017–16</td>
</tr>
<tr>
<td></td>
<td>GEM</td>
<td>22</td>
<td>4.0</td>
<td>&lt;0.078–370</td>
</tr>
<tr>
<td></td>
<td>Pt</td>
<td>0.13</td>
<td>0.012</td>
<td>&lt;0.00034–2.4</td>
</tr>
<tr>
<td></td>
<td>5FU</td>
<td>10</td>
<td>1.6</td>
<td>&lt;0.078–98</td>
</tr>
</tbody>
</table>

*Cisplatin, carboplatin, oxaliplatin, and nedaplatin were present in Hospital A.

bMean score ≤80%.

cMean score >80%.

dThe limit of detection of CP, GEM, Pt, and 5FU were 1.0, 300, 2.0, and 300 ng/wipe, respectively.

emann–Whitney’s U-test (nonattainment versus attainment periods).
was higher than 80%. These findings suggest that it is imperative not only to institute and revise drug-handling manuals but also to regularly train pharmacists on the checklist items in order to decrease the contamination levels of drugs within the workplace environment.

In addition to the workplace contamination (i.e. wipe test) findings, urine tests in pharmacists who prepared antineoplastic drugs at Hospital A confirmed that they were being exposed to both CP and 5FU. Furthermore, increasing the score above 80% appeared to have decreased the occupational exposure levels of pharmacists to CP and 5FU, as confirmed by the decreases in urinary CP and AFBA levels. Previous reports have detected urinary AFBA in urine samples of pharmaceutical plant workers and healthcare workers (Sessink et al., 1994; Rubino et al., 2006; Ndaw et al., 2010).

Table 3. Summary of the results of the present and previous studies.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Working surface of BSC (ng/cm²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.39</td>
<td>–</td>
<td>N.D.–32.18</td>
<td>Connor et al. (1999)</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>–</td>
<td>N.D.–3.63</td>
<td>Vandenbroucke and Robays (2001)</td>
</tr>
<tr>
<td></td>
<td>6.3</td>
<td>0.5</td>
<td>&lt;0.5–17.2</td>
<td>Sessink et al. (2011)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.3</td>
<td>&lt;0.036–41</td>
<td>Present study (nonattainment period)</td>
</tr>
<tr>
<td><strong>Front side of air grille of BSC (ng/cm²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.08</td>
<td>–</td>
<td>N.D.–27</td>
<td>Sessink et al. (1992b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.3</td>
<td>&lt;1.8–56.6</td>
<td>Sessink et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>9.4</td>
<td>&lt;0.15–98</td>
<td>Present study (nonattainment period)</td>
</tr>
</tbody>
</table>

*not detected.
However, the present study is the first report to demonstrate a relationship between urinary AFBA and the application of control measures.

We are often asked by pharmacy managers to advise them on the threshold level that they should set for antineoplastic drug exposure. However, it is difficult to set a threshold, as many antineoplastic drugs are carcinogens. Furthermore, primary cancer caused by alkylating drugs was found to be due to damage to Chromosomes 5 and 7 (Pedersen-Bjergaard et al., 2002). Interestingly, McDiarmid et al. reported that Chromosomes 5 and 7 showed more damage in pharmacists who prepared antineoplastic drugs than in those who did not prepare such drugs (McDiarmid et al., 2010). Despite the fact that these pharmacists prepared antineoplastic drugs according to the recommended standard methods outlined in the guidelines, they were still exposed to antineoplastic drugs in the workplace.

Thus, based on the findings of these studies, all hospitals must aim to decrease the levels of contamination and exposure to antineoplastic drugs until they are undetectable, in part, by using the checklist outlined in the present study. Sessink et al. (Sessink et al., 2011) reported that a closed-system device prevented spills and reduced the contamination levels of CP, ifosfamide, and 5FU at 22 hospitals, suggesting that all cytotoxic drugs, not just CP, need to be prepared within a closed-system device.

In Hospital A, by December 2008, most of the measures had been implemented. Regarding the basis of the aimed score of 80%, we had only our previous study for reference (Yoshida et al., 2011b). The contamination and exposure levels of the group with mean score lower than 60% (October 2007: 37.4%; and February 2008: 41.4%) was compared with those of the group with mean score higher than 60% (December 2010: 66.8%; February 2011: 80.6%; and June 2011: 80.6%). The contamination level was reduced statistically in the group higher than 60%. From this result, these control measures seemed to reduce the contamination level of antineoplastic drugs. However, exposure level of AFBA was not reduced statistically in the group with score higher than 60% ($P = 0.301$).

In conclusion, by increasing the score above 80%, hospitals can decrease contamination and levels of exposure to antineoplastic drugs. The scores of the items on the checklist appeared to adequately reflect the condition of the control measures, as increases in all five items were associated with reductions in the contamination and exposure levels for all drugs.

### SUPPLEMENTARY DATA

Supplementary data can be found at http://annhyg.oxfordjournals.org/.

### FUNDING


### REFERENCES


