Comparison of Contamination Levels on the Exterior Surfaces of Vials Containing Platinum Anticancer Drugs in Japan

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Contamination of the external surface of anticancer drug vials supplied to hospital pharmacies has been
recognized as a potential health hazard. The aim of this study was to investigate the levels of contamination
on the exterior surface of vials containing platinum anticancer drugs in Japan. Platinum contamination on
the exterior surface of vials containing cisplatin or carboplatin was examined using products commercially
available in Japan. Cisplatin vials from 42 batches (2 drug contents, 10 products and 5 manufacturers) and
carboplatin vials from 28 batches (3 drug contents, 7 products and 3 manufacturers) were used. Five vials
were randomly sampled from each batch. Exterior contamination levels of 0.070–144 ng/vial as cisplatin and
0.21–1630 ng/vial as carboplatin were detected. Significant differences in the levels of contamination among
the batch numbers were observed in 6 of 10 cisplatin products and 6 of 7 carboplatin products. Significant
differences in the levels of contamination were observed in 3 cisplatin products with different contents of
drug within the vials and 1 carboplatin product with different contents of drug within the vials. Significant
differences in the contamination levels among the cisplatin manufacturers but not carboplatin manufacturers
were observed. The degree of contamination of the carboplatin products was significantly higher than that of
the cisplatin products. In conclusion, external contamination was confirmed in all cisplatin and carboplatin
vials tested. The degree of contamination was different among different batch numbers, drug contents, man-
ufacturers, and platinum anticancer drug.

Key words platinum anticancer drug; product contamination; occupational exposure; vial contamination

A growing number of anticancer drugs have been identified
by the International Agency for Research on Cancer (IARC)
as known or suspected human carcinogens.1) Recently, occupa-
tional exposure of healthcare workers to anticancer drugs has
been recognized as a potential health hazard.2) Occupational
exposure can occur during receipt of a pharmaceutical product
or its storage, preparation, administration, and disposal. Some
reports have documented workplace contamination and occupa-
tional exposure to anticancer drugs via these routes in hos-
pital settings.1)–7) These reports were centered on the exposure
of oncology ward staff administering the drugs and pharmacy
staff who prepare and pack the prescriptions.

Contamination on the exterior surface of vials containing
anticancer drugs is a problem since it is a potential health
hazard.8)–10) Exterior contamination on platinum anticancer drug
vials supplied to hospital pharmacies was also confirmed in
earlier reports.11)–13) Platinum anticancer drugs such as cis-
platin and carboplatin play a major role in the treatment of
various malignancies, and large amounts of these drugs are
routinely handled in hospital pharmacies. They are known to
induce apoptosis in neoplastic cells by binding to nuclear
dNA and they possess toxicity and carcinogenicity in normal
cells.14) Cisplatin is classified into Group 2A in the IARC
Monographs, meaning it is probably carcinogenic to humans.1) Carboplatin, a platinum analogue with a distinctively different
toxicity profile from cisplatin, is also believed to play a role in
carcinogenesis.

Even though the manufacturing environment of anticancer
drugs is strictly controlled for chemical hazards, several stud-
ies have been published on the cytotoxic effects of exposure
to hazardous drugs in manufacturing plants.15,16) A few studies
have demonstrated cross contamination on the exterior of anti-
cancer drug vials.8,12) This means that contamination occurred
during the manufacturing process. The sources of contamination
have not been fully revealed, but could be associated with
leakage during filling, improper and inadequate vial cleaning
after filling, or accidental leakage during transport and distri-
bution.

Although occupational exposure to an anticancer drug is
affected by its chemical properties such as volatility, molecular
weight, and liposolubility, workplace contamination should be
minimized as much as possible.17) Contamination present
on the exterior surface of a vial containing anticancer drugs
has been a focus of attention in the handling of products in
hospital settings.8,18) There are no regulatory requirements
regarding maximal permissible levels of contamination on the
exterior of anticancer drug vials, and no previous studies have
examined contamination existing on the external surface
of vials of commercial products. Contamination of anticancer
drug vials delivered to hospital pharmacies needs to be as-
essed as a potential health hazard.

The aim of this study was to investigate the degree of con-
tamination of the external surface of cisplatin and carboplatin
vials. We assessed the degree of external contamination according
to the batch number, drug content within the vial, pharmaceu-
tical manufacturer, and type of platinum anticancer drug.

The authors declare no conflict of interest.

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**MATERIALS AND METHODS**

**Study Design** The investigation of platinum contamination on the exterior surface of the cisplatin and carboplatin vials was performed using the products delivered to four hospital pharmacies in Japan (Hamamatsu University Hospital, Seirei Hamamatsu General Hospital, Hamamatsu Medical Center, and Iwata City Hospital). Randa® (10, 50 mg, Nippon Kayaku Co., Ltd., Tokyo), Briplatin® (10, 50 mg, Bristol-Myers Squibb, Tokyo), Platosin® (10, 50 mg, Kyowa Hakko Kirin Co., Ltd., Tokyo), Cisplatin, Maruko (10, 50 mg, Yakult Honsha Co., Ltd., Tokyo) and Cisplatin, Nichi-iko (10, 50 mg, Nichi-iko Pharmaceutical Co., Ltd., Toyama, Japan) were selected as cisplatin vials. The carboplatin products were Paraplatin® (150, 450 mg, Bristol-Myers Squibb), Carboplatin, NK (50, 150, 450 mg, Nippon Kayaku Co., Ltd.) and Carboplatin, Sandoz (50, 150 mg, Sandoz, Tokyo). Platosin®, Cisplatin, Maruko, Cisplatin, Nichi-iko, Carboplatin, NK and Carboplatin, Sandoz are generic drugs. The concentrations of cisplatin and carboplatin in the products were 0.5 and 10 mg/mL, respectively. Each vial among the batch numbers was determined by the same investigator.

**Wiping Method** Platinum contamination on the exterior surface of the drug vials was wiped as previously described. Seventy percent propan-2-ol was used as the wiping solution of carboplatin vials. The head of a swab was moistened on one side with wiping solution. The lid, bottom and side of the drug vials were wiped once using the wet side and then again with the dry side of the swab. After cutting off the handle of the swab, the head paddle was dipped in a tube containing acetonitrile and ultra-pure water.

**Determination of the Platinum Anticancer Drug Levels** Cisplatin and carboplatin were purchased from Sigma Aldrich (St. Louis, MO, U.S.A.). Gold solution as an internal standard and N,N-diethyldithiocarbamate (DDTC) were obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Seventy percent propan-2-ol was used as the wiping solution of carboplatin vials. The head of a swab (Large Alpha® sampling swab, ITW Texwipe, Mahwah, NJ, U.S.A.) was moistened on one side with wiping solution. The lid, bottom and side of the drug vials were wiped once using the wet side and then again with the dry side of the swab. After cutting off the handle of the swab, the head paddle was dipped in a tube containing acetonitrile and ultra-pure water.

**Results**

**Study Demographics** This study included 42 batches of cisplatin products: 6 batches each of 10 mg and 50 mg Randa®, 5 batches of 10 mg and 6 batches of 50 mg Briplatin®, 3 batches each of 10 mg and 50 mg Platosin®, 4 batches each of 10 mg and 50 mg Cisplatin, Maruko, and 2 batches of 10 mg and 3 batches of 50 mg Cisplatin, Nichi-iko. A total of 28 batches of carboplatin products were studied: 5 batches of 10 mg and 4 batches of 450 mg Paraplatin®, 3 batches of 50 mg, 6 batches of 150 mg, and 3 batches of 450 mg Carboplatin, NK, and 3 batches of 50 mg and 4 batches of 150 mg Carboplatin, Sandoz.

**Contamination Levels on Vial Exterior** Figure 1 shows the contamination levels of the cisplatin and carboplatin vials. Contamination of the external surfaces of all 350 cisplatin and carboplatin vials (42 batches of cisplatin from 5 manufacturers and 28 batches of carboplatin from 3 manufacturers) was detected, and the levels were 0.070–144 ng as cisplatin and 0.21–1630 ng as carboplatin.

**Inter-Batch Differences** Significant differences compared to other batches were observed in the contamination levels of 10 mg (p=0.029) and 50 mg Randa®, 10 mg Briplatin® (p=0.038), 10 mg Platosin® (p=0.005), 50 mg Cisplatin, Maruko (p=0.001), and 10 mg Cisplatin, Nichi-iko (p=0.008) (Fig. 1). No significant differences in the exterior contamination levels of 50 mg Briplatin® (p=0.163), 50 mg Platosin® (p=0.733), 10 mg Cisplatin, Maruko (p=0.131), and 50 mg Cisplatin, Nichi-iko (p=0.185) were observed among the different batches examined. Among the carboplatin products, significant differences were found in the exterior contamination levels of 150 mg (p<0.001) and 450 mg (p<0.001) Paraplatin®, 50 mg (p=0.009) and 150 mg (p<0.001) Carboplatin, NK and 50 mg (p=0.027) and 150 mg (p=0.003) Carboplatin, Sandoz compared to the other batches. There was no significant difference in external contamination of 450 mg Carboplatin, NK (p=0.174) among the batches studied.

**Differences in Contamination according to Drug Content** Significant differences in the exterior contamination levels for different contents of Randa® (p<0.001), Briplatin® (p<0.001) and Platosin® (p=0.005) were observed (Table 1), while no significant differences were observed for different contents of Cisplatin, Maruko (p=0.445) and Cisplatin, Nichi-iko (p=0.461). Among the carboplatin products, a significant difference in the level of contamination was observed between the different contents of Paraplatin® (p=0.025) (Table 2). There were no significant differences in the contamination levels for different contents of drug in the Carboplatin, NK (p=0.610) and Carboplatin, Sandoz vials (p=0.179). After normalization for the content of...
cisplatin within the vials, significant differences in contamination levels were observed for Randa® ($p=0.002$), Cisplatin, Maruko ($p=0.003$) and Cisplatin, Nichi-iko ($p=0.001$) (Table 3), but not for Briplatin® ($p=0.514$) and Platosin® ($p=1.000$).

After normalization for the content of carboplatin within the vials, significant differences in contamination levels were
observed for Carboplatin, NK ($p=0.001$) and Carboplatin, Sandoz ($p=0.001$) (Table 4), but not for Paraplatin® ($p=0.851$).

**Differences in Contamination among Pharmaceutical Manufacturers** Significant differences in the levels of contamination of the external surface of the vials among the different manufacturers of cisplatin products were observed ($p<0.001$) (Table 1) while no significant differences were observed among the carboplatin manufacturers ($p=0.808$) (Table 2). After normalization for the content of cisplatin within the vials, significant differences in the contamination levels among the different manufacturers were observed ($p<0.001$) (Table 3). After normalization for carboplatin content, no differences in contamination levels were observed among the carboplatin manufacturers ($p=0.114$) (Table 4).

**Platinum Anticancer Drugs** The median levels of cisplatin and carboplatin contamination were 1.44 ng (IQR, 0.595–4.89 ng) and 3.80 ng (IQR, 1.60–11.5 ng), respectively. The degree of contamination of the carboplatin products was significantly higher than that of the cisplatin products ($p<0.001$). After normalization for drug content and volume, the median levels of contamination on the external vial surface were 60.9 pg/vial mg (IQR, 26.6–162 pg/vial mg) and 30.5 pg/vial mL (IQR, 13.3–81.1 pg/vial mL) as cisplatin and 23.5 pg/vial mg (IQR, 10.3–74.9 pg/vial mg) and 235 pg/vial mL (IQR, 103–749 pg/vial mL) as carboplatin, respectively. Significant differences in the contamination levels after normalization for drug content and volume were observed between the cisplatin and carboplatin vials ($p<0.001$ and $p<0.001$, respectively).

## DISCUSSION

Although contamination of the outside of anticancer drug vials dispensed by hospital pharmacies has been recognized as a potential health hazard, no previous study has adequately examined the issue. This study investigated the contamination levels on the outside surface of vials containing platinum

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### Table 1. Contamination Levels Detected on the Exterior of Cisplatin Vials

<table>
<thead>
<tr>
<th>Cisplatin injections</th>
<th>Content (mg)</th>
<th>Drug price (JPY)</th>
<th>Vial ($n$)</th>
<th>Contamination levels (ng/vial)</th>
<th>Minimum</th>
<th>First quartile</th>
<th>Median</th>
<th>Third quartile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randa® ($p&lt;0.001$)</td>
<td>Total —</td>
<td>—</td>
<td>60</td>
<td></td>
<td>0.168</td>
<td>0.550</td>
<td>0.957</td>
<td>1.59</td>
<td>17.0</td>
</tr>
<tr>
<td></td>
<td>10 3166</td>
<td>30</td>
<td></td>
<td></td>
<td>0.168</td>
<td>0.486</td>
<td>0.579</td>
<td>0.920</td>
<td>3.12</td>
</tr>
<tr>
<td></td>
<td>50 13845</td>
<td>50</td>
<td></td>
<td></td>
<td>0.435</td>
<td>0.994</td>
<td>1.56</td>
<td>3.13</td>
<td>17.0</td>
</tr>
<tr>
<td>Briplatin® ($p&lt;0.001$)</td>
<td>Total —</td>
<td>55</td>
<td></td>
<td></td>
<td>0.0701</td>
<td>0.252</td>
<td>0.723</td>
<td>1.96</td>
<td>13.6</td>
</tr>
<tr>
<td></td>
<td>10 3166</td>
<td>25</td>
<td></td>
<td></td>
<td>0.0701</td>
<td>0.173</td>
<td>0.244</td>
<td>0.474</td>
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<td></td>
<td>50 13531</td>
<td>30</td>
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<td></td>
<td>0.381</td>
<td>0.770</td>
<td>1.58</td>
<td>3.65</td>
<td>13.6</td>
</tr>
<tr>
<td>Platosin® ($p=0.005$)</td>
<td>Total —</td>
<td>30</td>
<td></td>
<td></td>
<td>0.186</td>
<td>1.29</td>
<td>5.01</td>
<td>9.57</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>10 2610</td>
<td>15</td>
<td></td>
<td></td>
<td>0.186</td>
<td>0.760</td>
<td>1.29</td>
<td>5.98</td>
<td>14.5</td>
</tr>
<tr>
<td></td>
<td>50 10949</td>
<td>15</td>
<td></td>
<td></td>
<td>1.34</td>
<td>4.89</td>
<td>5.89</td>
<td>15.5</td>
<td>144</td>
</tr>
<tr>
<td>Cisplatin, Maruko ($p=0.445$)</td>
<td>Total —</td>
<td>40</td>
<td></td>
<td></td>
<td>0.379</td>
<td>1.25</td>
<td>3.12</td>
<td>5.21</td>
<td>33.6</td>
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<tr>
<td></td>
<td>10 1454</td>
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<td>0.599</td>
<td>1.68</td>
<td>2.80</td>
<td>3.44</td>
<td>7.90</td>
</tr>
<tr>
<td></td>
<td>50 6502</td>
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<td></td>
<td></td>
<td>0.379</td>
<td>0.613</td>
<td>4.70</td>
<td>7.65</td>
<td>33.6</td>
</tr>
<tr>
<td>Cisplatin, Nichi-iko ($p=0.461$)</td>
<td>Total —</td>
<td>25</td>
<td></td>
<td></td>
<td>0.766</td>
<td>1.31</td>
<td>2.81</td>
<td>15.0</td>
<td>38.6</td>
</tr>
<tr>
<td></td>
<td>10 1306</td>
<td>10</td>
<td></td>
<td></td>
<td>1.17</td>
<td>1.32</td>
<td>4.57</td>
<td>21.0</td>
<td>38.6</td>
</tr>
<tr>
<td></td>
<td>50 5492</td>
<td>15</td>
<td></td>
<td></td>
<td>0.766</td>
<td>1.27</td>
<td>2.81</td>
<td>11.5</td>
<td>27.8</td>
</tr>
</tbody>
</table>

The $p$-values shown in the table mean the statistical differences in contamination levels according to drug content within the vials. Significant differences were observed in the contamination levels among the cisplatin manufacturers ($p<0.001$). Drug price at April 2010. JPY, Japanese yen. 1 $US is approximately equal to 80 JPY as of July 2012.

### Table 2. Contamination Levels Detected on the Exterior of Carboplatin Vial

<table>
<thead>
<tr>
<th>Carboplatin injections</th>
<th>Content (mg)</th>
<th>Drug price (JPY)</th>
<th>Vial ($n$)</th>
<th>Contamination levels (ng/vial)</th>
<th>Minimum</th>
<th>First quartile</th>
<th>Median</th>
<th>Third quartile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraplatin® ($p=0.025$)</td>
<td>Total —</td>
<td>—</td>
<td>45</td>
<td></td>
<td>0.483</td>
<td>1.60</td>
<td>4.34</td>
<td>11.8</td>
<td>793</td>
</tr>
<tr>
<td></td>
<td>150 16352</td>
<td>25</td>
<td></td>
<td></td>
<td>0.483</td>
<td>1.17</td>
<td>2.10</td>
<td>9.79</td>
<td>44.5</td>
</tr>
<tr>
<td></td>
<td>450 42322</td>
<td>20</td>
<td></td>
<td></td>
<td>0.891</td>
<td>3.16</td>
<td>7.67</td>
<td>25.7</td>
<td>793</td>
</tr>
<tr>
<td>Carboplatin, NK ($p=0.610$)</td>
<td>Total —</td>
<td>60</td>
<td></td>
<td></td>
<td>0.205</td>
<td>1.76</td>
<td>4.05</td>
<td>11.1</td>
<td>1630</td>
</tr>
<tr>
<td></td>
<td>50 4941</td>
<td>15</td>
<td></td>
<td></td>
<td>0.662</td>
<td>1.43</td>
<td>2.41</td>
<td>12.6</td>
<td>22.7</td>
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<td>150 12103</td>
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<td></td>
<td>0.205</td>
<td>2.12</td>
<td>4.05</td>
<td>22.3</td>
<td>1630</td>
</tr>
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<td>450 29394</td>
<td>15</td>
<td></td>
<td></td>
<td>1.17</td>
<td>1.74</td>
<td>4.55</td>
<td>6.17</td>
<td>99.8</td>
</tr>
<tr>
<td>Carboplatin, Sandoz ($p=0.179$)</td>
<td>Total —</td>
<td>35</td>
<td></td>
<td></td>
<td>0.862</td>
<td>1.44</td>
<td>2.80</td>
<td>10.3</td>
<td>522</td>
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<td>1.37</td>
<td>2.76</td>
<td>6.86</td>
<td>25.5</td>
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</table>

The $p$-values shown in the table mean the statistical differences in contamination levels according to drug content within the vials. No significant differences were observed in the contamination levels among the carboplatin manufacturers ($p=0.808$). Drug price at April 2010. JPY, Japanese yen. 1 $US is approximately equal to 80 JPY as of July 2012.
anticancer drugs. Significant differences were found in the levels of contamination of cisplatin and carboplatin vials according to the batch number, drug content, and manufacturer. In addition, the degree of contamination found on the carboplatin vials was higher than that on the cisplatin vials. These findings suggest that the contamination levels vary among different batches, drug contents, manufacturers, and platinum anticancer drug. To the best of our knowledge, this is the first report in Japan to assess the degree of contamination present on the outside of vials according to the batch number, drug content, manufacturer, and platinum anticancer drug.

Exterior contamination was confirmed in all cisplatin and carboplatin vials investigated. Our previous analytical validation report demonstrated differences in exterior contamination levels between vials filled and not filled with a platinum anticancer drug.\(^2\) This means that the source of the platinum contamination on the outside of the drug vials was the cisplatin and carboplatin. In the present study, contamination levels of 0.070–144 ng as cisplatin and 0.21–1630 ng as carboplatin were detected on 350 vials from 42 batches and 5 manufacturers of cisplatin and from 28 batches and 3 manufacturers of carboplatin. Nygren et al. also detected 0.2–99 ng of cisplatin on the exteriors of 6 of 6 cisplatin vials from 3 manufacturers.\(^3\) Mason et al. detected exterior contamination levels of less than 9 ng in 13% of cisplatin vials (30 vials from 1 manufacturer) and 7–251 ng in all carboplatin vials (30 vials from 2 manufacturers).\(^4\) Connor et al. also found less than 256 ng in each of 218 cisplatin vials in 3 batches from 1 manufacturer.\(^5\) The present study investigated a larger number of vials, batches, and manufacturers, resulting in a slightly wider range of contamination levels.

Among different batches of the same drug, differences in exterior contamination levels were observed in 6 of 10 cisplatin products with different drug contents and 6 of 7 carboplatin products with different drug contents. Differences were identified for all manufacturers studied. Our data strongly suggest that the plants that manufactured these anticancer drugs are contaminated. Two previous reports have

Table 3. Vial Exterior Contamination Levels Normalized for Cisplatin Content

<table>
<thead>
<tr>
<th>Cisplatin injections</th>
<th>Content (mg)</th>
<th>Vial (n)</th>
<th>Minimum</th>
<th>First quartile</th>
<th>Median</th>
<th>Third quartile</th>
<th>Maximum</th>
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</thead>
<tbody>
<tr>
<td>Randa(^6)</td>
<td>Total 60</td>
<td></td>
<td>8.69</td>
<td>30.3</td>
<td>48.6</td>
<td>89.3</td>
<td>339</td>
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<td>10 30</td>
<td></td>
<td>16.8</td>
<td>48.6</td>
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<td>50 30</td>
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<td>8.69</td>
<td>19.9</td>
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<td>Briplatin(^6)</td>
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<td>7.01</td>
<td>15.8</td>
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<td>31.6</td>
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<td>Platinol(^7)</td>
<td>Total 30</td>
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<td>76.0</td>
<td>118</td>
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<td>18.6</td>
<td>76.0</td>
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<td>50 15</td>
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<td>26.8</td>
<td>97.8</td>
<td>118</td>
<td>310</td>
<td>2875</td>
</tr>
<tr>
<td>Cisplatin, Maruko</td>
<td>Total 40</td>
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<td>7.59</td>
<td>75.6</td>
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<td>332</td>
<td>790</td>
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<td>59.9</td>
<td>168</td>
<td>280</td>
<td>344</td>
<td>790</td>
</tr>
<tr>
<td></td>
<td>50 20</td>
<td></td>
<td>7.59</td>
<td>12.2</td>
<td>94.0</td>
<td>153</td>
<td>671</td>
</tr>
<tr>
<td>Cisplatin, Nichi-iko</td>
<td>Total 25</td>
<td></td>
<td>15.3</td>
<td>49.9</td>
<td>119</td>
<td>394</td>
<td>3860</td>
</tr>
<tr>
<td></td>
<td>10 10</td>
<td></td>
<td>117</td>
<td>132</td>
<td>456</td>
<td>2104</td>
<td>3860</td>
</tr>
<tr>
<td></td>
<td>50 15</td>
<td></td>
<td>15.3</td>
<td>25.5</td>
<td>56.2</td>
<td>230</td>
<td>556</td>
</tr>
</tbody>
</table>

The \(p\)-values shown in the table mean the statistical differences in contamination levels according to drug content within the vials. Significant differences were observed in the contamination levels among the cisplatin manufacturers (\(p<0.001\)).

Table 4. Vial Exterior Contamination Levels Normalized for Carboplatin Content

<table>
<thead>
<tr>
<th>Carboplatin injections</th>
<th>Content (mg)</th>
<th>Vial (n)</th>
<th>Minimum</th>
<th>First quartile</th>
<th>Median</th>
<th>Third quartile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraplatin(^8)</td>
<td>Total 45</td>
<td></td>
<td>1.98</td>
<td>7.79</td>
<td>16.5</td>
<td>65.3</td>
<td>1764</td>
</tr>
<tr>
<td></td>
<td>150 25</td>
<td></td>
<td>3.22</td>
<td>7.79</td>
<td>14.0</td>
<td>65.3</td>
<td>297</td>
</tr>
<tr>
<td></td>
<td>450 20</td>
<td></td>
<td>1.98</td>
<td>7.03</td>
<td>17.0</td>
<td>57.0</td>
<td>1764</td>
</tr>
<tr>
<td>Carboplatin, NK(^9)</td>
<td>Total 60</td>
<td></td>
<td>1.37</td>
<td>11.6</td>
<td>26.6</td>
<td>103</td>
<td>10867</td>
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<tr>
<td></td>
<td>50 15</td>
<td></td>
<td>13.2</td>
<td>28.5</td>
<td>48.2</td>
<td>251</td>
<td>455</td>
</tr>
<tr>
<td></td>
<td>150 30</td>
<td></td>
<td>1.37</td>
<td>14.1</td>
<td>27.0</td>
<td>149</td>
<td>10867</td>
</tr>
<tr>
<td></td>
<td>450 15</td>
<td></td>
<td>2.60</td>
<td>3.87</td>
<td>10.1</td>
<td>13.7</td>
<td>222</td>
</tr>
<tr>
<td>Carboplatin, Sandoz(^9)</td>
<td>Total 35</td>
<td></td>
<td>5.75</td>
<td>16.9</td>
<td>30.4</td>
<td>157</td>
<td>10446</td>
</tr>
<tr>
<td></td>
<td>50 15</td>
<td></td>
<td>21.1</td>
<td>34.9</td>
<td>95.2</td>
<td>540</td>
<td>10446</td>
</tr>
<tr>
<td></td>
<td>150 20</td>
<td></td>
<td>5.75</td>
<td>9.14</td>
<td>18.4</td>
<td>45.7</td>
<td>170</td>
</tr>
</tbody>
</table>

The \(p\)-values shown in the table mean the statistical differences in contamination levels according to drug content within the vials. No significant differences were observed in the contamination levels among the carboplatin manufacturers (\(p=0.114\)).
described cytotoxic exposure of workers to hazardous drugs in manufacturing plants.\textsuperscript{11,13} In addition, differences in contamination levels among vials were also observed in batches with higher contamination levels. The levels of contamination present on the outside surface of vials should be assessed using multiple batches with random samplings due to inter- and intra-batch differences. Large variations were also observed in exterior contamination level within same batch. The wide range of exterior contamination levels within same batch may be associated with accidental leakage during the filling rather than cleaning processes.

Different levels of contamination were found in 3 of 5 cisplatin products and 1 of 3 carboplatin products with different drug contents within the vials. Connor \textit{et al.} reported that the exterior contamination levels increased as the content of cisplatin in the vials increased.\textsuperscript{13} In the present study, the contamination level increased as the drug content increased in 4 cisplatin products and 1 carboplatin product. Vials with a higher drug content did not always have a higher level of contamination. The wide range of exterior contamination levels may have occurred due to contamination that originated from accidental leakage during the filling, cleaning, or transferring processes.\textsuperscript{9} After normalization for drug content, differences were found in 3 of 5 cisplatin products and in 2 of 3 carboplatin products. Connor \textit{et al.} also reported differences in the levels of contamination after normalization for drug content.\textsuperscript{13} The differences in contamination levels after normalization for drug content indicate that the levels of vial surface contamination are not always dependent on the drug content of each anticancer drug.

The degree of contamination on the exterior of cisplatin products was different among the various manufacturers examined while the degree of contamination on the exterior of carboplatin products was not. After normalization for drug content, the differences were observed only in cisplatin products. Further investigations with a larger number of batches and manufacturers of carboplatin products are needed to identify the differences among the various manufacturers. Our data suggested that the level of contamination could be related to the maximum permissible value for each manufacturer, and the unique decontamination techniques employed by each manufacturer may be responsible for the wide range of contamination levels seen in the products investigated. However, it is difficult to gather the information from manufacturers regarding decontamination technique of the vial exterior of each anticancer drug. To date, no regulatory guidelines have been published regarding vial decontamination after filling. Good manufacturing practices are similar in many countries owing to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This supports our finding that the degree of exterior contamination in the present study is comparable to that in earlier reports.\textsuperscript{11–13}

The degree of contamination on the outside of carboplatin vials was higher than that of cisplatin vials. Carboplatin vials containing higher contents of drug had higher contamination levels. The level of contamination on cisplatin vials after normalization of the drug content was higher than that on carboplatin vials, while the level of contamination after normalization of drug volume showed the opposite results. The drug concentration in the carboplatin vials (10mg/mL) was 20-fold higher than that of the cisplatin vials (0.5mg/mL). The correlation between the drug content and volume can most likely explain the difference in the assessments.

The quality assurance of a pharmaceutical product in Japan is implemented in accordance with the Japanese Pharmacopoeia or International Conference on Harmonization (ICH). The manufacturing environment for anticancer drugs in particular is strictly controlled in accordance with ICH Q7A.\textsuperscript{21} Contamination on the outside of anticancer drug products has been recognized as a potential health hazard. However, no regulatory guidelines have been published for hazard control of the product itself. Products possessing lower contamination levels would be considered to be of superior quality. Our study suggests that the contamination of vial exteriors is available as the quality index of anticancer products. Application of a protective film such as Onco-Tain\textsuperscript{TM} (Hospira, Inc., Lake Forest, IL, U.S.A.) may have quality advantages with respect to hazard control. The degree of external contamination of vials of anticancer products may be a determining factor for the acceptance by a hospital of an anticancer product.

The degree of exterior contamination detected in Randa\textsuperscript{6} and Briplatin\textsuperscript{8} vials was lower than that of the other cisplatin products (Table 1). In contrast, no differences were identified in the degree of exterior contamination among the 3 carboplatin products (Table 2). The drug prices for carboplatin products were not related to the degree of contamination. Further investigations with a larger number of batches and manufacturers of carboplatin products are needed to identify the relationships between drug price and contamination levels. The manufacturing techniques of anticancer drug employed by each manufacturer are not associated with the drug prices in Japan. In Japan, the drug prices were determined by the market prices. Although anticancer drug products with lower prices cannot be produced by the inferior manufacturing techniques, cisplatin products with higher drug prices tend to be associated with lower levels of exterior contamination.

The United States Occupational Safety and Health Administration has set threshold limit values for platinum salts in workplace air.\textsuperscript{22} Some studies have centered on workplace contamination and occupational exposure to anticancer drugs.\textsuperscript{7–9} Occupational exposure to an anticancer drug is affected by its chemical properties such as volatility, molecular weight, and liposolubility.\textsuperscript{17} Schierl \textit{et al.} proposed threshold guidance values for contamination monitoring of anticancer drugs in pharmacy workplaces.\textsuperscript{23} Information on the long-term toxicity of many anticancer drugs in humans is deficient.\textsuperscript{24,25} Some anticancer drugs are identified by the IARC as known or suspected human carcinogens.\textsuperscript{1} In hospital settings, occupational exposure to anticancer drugs should be minimized to the greatest extent possible. Workplace contamination was detected on all surfaces in the pharmacies with high levels on storage shelves and floors. The median values for the different locations ranged from 0.20 to 1.70 pg as platinum/\textit{cm}\textsuperscript{2}.\textsuperscript{23} In the present study, the median levels of cisplatin and carboplatin contamination were 1.44 ng and 3.80 ng/vial, respectively. Contaminations on cisplatin and carboplatin vials were higher than that on all locations in pharmacies. These data support the necessity of promotion of safe handling guidelines for anticancer drugs.\textsuperscript{18,19}

The present study has several limitations. First, our survey lacks long-term data. We studied contamination over a
one-year period. Contamination levels may change with improvements in the manufacturing process. Second, the most reasonable corrections reflecting the degree of contamination have not been documented in this report. To date, no regulatory guidelines have been published on corrections reflecting the degree of contamination. Our data indicate that the corrections influence the evaluation of vial exterior contamination. The degree of exterior contamination may be also affected by the corrections. In this study, the exterior contamination levels were not corrected for vial exterior surface area. Correction for the vial exterior surface area would most likely yield a similar tendency to that for drug volume. Third, the present report does not include the technical suggestion to reduce in the contamination of vial exterior surface. The decontamination techniques are needed to examine because contamination of the outside of anticancer drug vials dispensed by hospital pharmacies has been recognized as a potential health hazard.

CONCLUSION

The present study confirmed the presence of contamination on the outside of all cisplatin vials from 42 batches and 5 manufacturers and all carboplatin vials from 28 batches and 3 manufacturers. The degree of contamination differed according to the batch number, drug content, manufacturer, and type of platinum anticancer drug.

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REFERENCES


