Antineoplastic Drug Monitoring

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Dr. Paul J.M. Sessink PhD

• 1980-1988 Chemistry
• 1988-1993 PhD study / Thesis
  “Monitoring of occupational exposure to antineoplastic drugs”
• 1995 Exposure Control B.V.
  Consultancy for monitoring of occupational exposure to antineoplastic drugs
  (sampling – analysis – advise)
• 1996 PhD Medical Sciences
Antineoplastic Drug Monitoring

• Introduction
  – Toxicity (genotoxic carcinogens)
  – Safety guidelines and personal protection
  – Directive EU carcinogenic compounds

• Monitoring
  – Environmental and biological monitoring
  – Cyto Wipe Kits and Cyto Urine Kit

• Environmental contamination (results from several studies)
  – Preparation: gloves, BSC, surface contamination

• Urine analysis

• Cancer risk

• Benchmarking model for environmental contamination

• Health based surface contamination limits

• Conclusions
# Toxicity of antineoplastic drugs

## Acute effects
- Irritation (skin, eyes)
- Alopecia
- Nausea
- Vomiting
- Diarrhea
- Organs (liver, kidney, bladder, lung)
- Bone marrow suppression

## Delayed effects
- Reproductive effects
  - Spontaneous abortions
  - Malformations off-spring
  - Low birth weight
  - Prolonged time to pregnancy
- Menstrual dysfunction
- Mutagenicity
- Carcinogenicity
  - Genotoxic/Non-genotoxic
  - IARC classification
Genotoxic carcinogens

Mechanism of action

→ Absence no-adverse-effect level supposed:

   *one molecule is able to induce cancer!*

→ Exposure has to be avoided
→ Workers need to be protected
→ Safety guidelines and protective measures
→ Monitoring of the workers
STRATEGY (decreasing priority)

1) replacement by a less toxic compound
   If not possible →
2) reduce sources of exposure
   If not possible →
3) ventilation
   If not possible →
4) personal protection
Carcinogenic Compounds
28 June 1990

STRATEGY FOR ANTINEOPLASTIC DRUGS

1) replacement by a less toxic compound
   → Impossible

2) reduce sources of exposure
   → Closed systems

3) ventilation
   → Clean rooms with BSCs

4) personal protection
   → Gloves, gowns, masks, special clothes, …
## Environmental and Biological Monitoring

**Environmental Monitoring**
- Measures the presence/release of the drug in the environment
- No information about uptake of the drug in the body of the worker
- No information about health-risk for the worker

**Biological Monitoring**
- Assessment of uptake of the drug in the body of the worker
- Estimation of health-risk for the worker
Monitoring antineoplastic drugs
Exposure Control B.V.

Environmental Monitoring

- Cyclophosphamide 0.1 ng/ml sample
- Ifosfamide 0.1 ng/ml sample
- 5-Fluorouracil 20 ng/ml sample
- Methotrexate 5 ng/ml sample
- Platin compounds (cis-platin & carbo-platin) 0.2 ng/ml sample
- Etoposide 50 ng/ml sample
- Mitomycine C 100 ng/ml sample

Analysis:
HPLC, GC-MSMS, Voltammetry
Monitoring antineoplastic drugs
Exposure Control B.V.

Biological Monitoring (urine)

- Cyclophosphamide +/- 0.1 ng/ml sample
- Ifosfamide +/- 0.1 ng/ml sample
- 5-Fluorouracil (a-fluoro-ß-alanine) 20 ng/ml sample

Analysis:
GC-MSMS
Cyto Wipe Kits – 4 types

- 6 x 2 = 12 tissues
- 6 droppers with 17 ml solution
- 6 containers, labels and plastic mini bags
- 6 pair of gloves
- registration form
- label address lab Exposure Control B.V.
- waterproof pen
- instruction of use
Cyto Urine Kit

This urine kit contains the materials to take 10 urine samples (24 hour period)

- 10 vacuette urine tubes and labels
- 1 urine transfer device
- measuring cup
- registration form
- label address lab of Exposure Control B.V.
- instructions of use
- waterproof pen
Sources of contamination and potential exposure

- External vial contamination
- Spillage during preparation and administration (handling technique)
- BSC/isolator
- Patient (urine, sweat, vomit, blood, faeces)
- Waste
- Laundry and clothing patient
Glove contamination during preparation of antineoplastic drugs

<table>
<thead>
<tr>
<th>Pair of gloves</th>
<th>Drug</th>
<th>N(pos)</th>
<th>Range (µg/pair)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Cyclophosphamide</td>
<td>8</td>
<td>1.5 – 9.6</td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil</td>
<td>11</td>
<td>21 – 620</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>2</td>
<td>220 – 1900</td>
</tr>
<tr>
<td>10</td>
<td>Cyclophosphamide</td>
<td>1</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil</td>
<td>10</td>
<td>16 – 1040</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>4</td>
<td>19 – 156</td>
</tr>
</tbody>
</table>

Conclusion: most gloves contaminated during preparation
# Contamination BSC

<table>
<thead>
<tr>
<th>Day</th>
<th>Before preparation</th>
<th>After preparation</th>
<th>After alcohol cleaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Drugs analyzed: cyclophosphamide - 5-fluorouracil - methotrexate

- one drug detected
- two drugs detected
- three drugs detected
- no drugs detected

**Conclusion:** contamination and ineffective cleaning procedure
Surface contamination with cyclophosphamide in preparation areas (ng/cm²)

*Connor et al., Am J Health-Syst Pharm 1999; 56:1427-32

<table>
<thead>
<tr>
<th>Description surface</th>
<th>Canada*</th>
<th>USA*</th>
<th>Belgium</th>
<th>Sweden</th>
<th>Germany</th>
<th>Netherlands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table top cyto preparation/BSC</td>
<td>0.01-2.63</td>
<td>0.05-40.13</td>
<td>0.13-6.61</td>
<td>4.74-15.32</td>
<td>14.02-14.22</td>
<td>0.01-1.16</td>
</tr>
<tr>
<td>Floor under BSC</td>
<td>0.05-0.32</td>
<td>0.03-2.40</td>
<td>0.05-0.55</td>
<td>1.79</td>
<td>0.05</td>
<td>0.01-0.03</td>
</tr>
<tr>
<td>Floor central preparation room</td>
<td>0.11-0.16</td>
<td>0.01-2.36</td>
<td>0.15-0.31</td>
<td>1.24</td>
<td>1.77</td>
<td>0.01-0.02</td>
</tr>
<tr>
<td>Table top not for cyto preparation</td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
<td>0.03-0.19</td>
<td>0.01-0.36</td>
</tr>
<tr>
<td>Floor entrance preparation room</td>
<td></td>
<td></td>
<td></td>
<td>0.52</td>
<td>0.16</td>
<td>0.01-0.02</td>
</tr>
<tr>
<td>Floor entrance preparation room/corridor</td>
<td>0.01-0.13</td>
<td>0.14-0.19</td>
<td>0.09</td>
<td></td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>
Contamination with cyclophosphamide (ng/cm²) in a clean room 1997-2004 (NL)

<table>
<thead>
<tr>
<th>Spot</th>
<th>1997 (n=4)</th>
<th>2002 (n=4)</th>
<th>2004 (n=8)</th>
<th>2004 (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface LAF left</td>
<td>ND - 0.10</td>
<td>ND - 0.01</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Airfoil LAF left</td>
<td>0.02 - 0.08</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Floor LAF left</td>
<td>ND – 0.01</td>
<td>ND - 0.01</td>
<td>ND – 0.01</td>
<td>ND</td>
</tr>
<tr>
<td>Surface LAF right</td>
<td>0.05 – 1.16</td>
<td>ND - 0.64</td>
<td>0.10 – 1.15</td>
<td>ND</td>
</tr>
<tr>
<td>Airfoil LAF right</td>
<td>1.52 – 7.71</td>
<td>ND - 0.22</td>
<td>ND - 0.03</td>
<td>ND</td>
</tr>
<tr>
<td>Floor LAF right</td>
<td>ND - 0.01</td>
<td>ND</td>
<td>ND - 0.01</td>
<td>ND</td>
</tr>
<tr>
<td>Table</td>
<td>ND - 0.02</td>
<td>ND</td>
<td>ND - 0.01</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: Not Detected

Conclusion: Reduction of contamination in time
Surface contamination with cyclophosphamide in preparation areas reduced with PhaSeal

*Sessink et al., submitted to Am J Health-Syst Pharm

<table>
<thead>
<tr>
<th>Surface</th>
<th>N</th>
<th>Min-Max</th>
<th>Median</th>
<th>Standard techniques</th>
<th>PhaSeal</th>
<th>PhaSeal</th>
<th>Standard techniques</th>
<th>PhaSeal</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSC surface</td>
<td>30</td>
<td>&lt; 0.01-17.19</td>
<td>&lt; 0.01-5.41</td>
<td>0.13</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC airfoil</td>
<td>26</td>
<td>&lt; 0.02-158.00</td>
<td>0.01-17.15</td>
<td>3.86</td>
<td>0.20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Floor in front BSC</td>
<td>29</td>
<td>&lt; 0.01-34.76</td>
<td>&lt; 0.01-16.33</td>
<td>0.14</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counter</td>
<td>29</td>
<td>&lt; 0.01-122.27</td>
<td>&lt; 0.01-0.90</td>
<td>0.03</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P < 0.0001
Cyclophosphamide (CP) in urine of technicians preparing cytotoxic drugs 1986-2002 (NL)

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of technicians</th>
<th>Collection period (days)</th>
<th>Mean amount CP in urine (µg/day)</th>
<th>Range CP (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>20</td>
<td>4</td>
<td>0.39</td>
<td>0 - 2.5</td>
</tr>
<tr>
<td>1992</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1992</td>
<td>18</td>
<td>1 – 2</td>
<td>0.05</td>
<td>0 - 0.5</td>
</tr>
<tr>
<td>1994</td>
<td>9</td>
<td>1 – 2</td>
<td>1.36</td>
<td>0 - 10.05</td>
</tr>
<tr>
<td>1995</td>
<td>8</td>
<td>8 – 16</td>
<td>0.18</td>
<td>0.01 - 0.53</td>
</tr>
<tr>
<td>1996</td>
<td>9</td>
<td>5</td>
<td>0.16</td>
<td>0 - 0.51</td>
</tr>
<tr>
<td>1997</td>
<td>4</td>
<td>2</td>
<td>0.013</td>
<td>0 - 0.04</td>
</tr>
<tr>
<td>1999</td>
<td>7</td>
<td>1 – 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2002</td>
<td>4</td>
<td>2</td>
<td>0.003</td>
<td>0 - 0.014</td>
</tr>
</tbody>
</table>
Additional cancer risk exposure to cyclophosphamide

- **Technicians**
  - 0.18 µg CP in urine/day
  - 1.4-10 extra cancer cases a million workers a year

- **Nurses**
  - 0.80 µg CP in urine/day
  - 10-50 extra cancer cases a million workers a year

- **Prohibitory risk level**
  - 100 extra cancer cases a million workers a year

- **Strive risk level**
  - 1 extra cancer case a million workers a year

**Conclusion**

strive risk level not achieved → too high exposure levels
Benchmarking model for environmental contamination

- Comparison of contamination with comparable reference studies
  - Per country
  - Preparation or administration
  - Per drug
    - Contamination level ng/cm² (low – medium – high)
    - Spread (no spread – some spread – totally spread)
- Ranking (high – medium – low)
- Long-term result: contamination will be reduced
# Health based (cancer) surface contamination limits for cyclophosphamide in hospitals

<table>
<thead>
<tr>
<th></th>
<th>Strive risk level</th>
<th>0.02 – 0.2</th>
<th>0.2 - 2</th>
<th>&gt; 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine CP (µg/24 hr)</td>
<td>&lt; 0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contamination CP (ng/cm²)</td>
<td>&lt; 0.1</td>
<td>0.1 – 1</td>
<td>1.0 – 10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>Action</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Now and then</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Conclusions

- Antineoplastic drugs are spread in the environment during preparation, administration, patient care and waste handling.
- Healthcare workers are exposed to antineoplastic drugs.
  - Current preparation and administration techniques need to be improved.
- The main exposure routes are:
  - Dermal uptake → contact with contaminated surfaces.
  - Inhalation → particles (vapors?).
- Depending on the level of exposure:
  → additional cancer risk for hospital workers handling antineoplastic drugs.
  → reproductive effects unknown (more sensitive?).
- Development of health based surface contamination limits is recommended for monitoring.
- Till then, a bench marking model is a good alternative to reduce environmental contamination.