The adverse health effects of occupational exposure to hazardous drugs

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For the past several decades, there has been growing concern regarding the safety and health of healthcare workers who are occupationally exposed to chemotherapy and other drugs. The activities that create greatest risk are preparing and administering antineoplastic agents, cleaning up chemotherapy spills, and handling patient excreta. This article will review the potential adverse health effects associated with handling these agents, including acute symptoms, reproductive health issues, and potential cancer development. Healthcare workers handling chemotherapeutic agents report an increased incidence of acute health symptoms such as nausea, vomiting, headaches, and hair loss. Additionally, many studies have identified an association between exposure to the drugs and adverse effects on reproductive health among female staff members, including infertility, preterm deliveries, spontaneous abortions, fetal abnormalities, and small-for-gestational-age births.

For the past decade, concern has been growing regarding the safety of healthcare workers who handle chemotherapy drugs. The handling of antineoplastic agents and other hazardous drugs has been an acknowledged occupational hazard to those healthcare personnel who work with these agents. Knowledge gained from studies conducted in the early 1980s has provided a wealth of information regarding the routes of exposure from these agents. An investigation has concluded that the probable hazardous drug exposure routes include dermal absorption, primarily from handling contaminated material; ingestion; and inhalation. In addition, many of these agents or their metabolites are found in patients’ excreta. This may expose personnel during the handling of the excreta.

Generally, the occupational activities that pose the greatest risk are preparing and administering antineoplastic agents, cleaning up chemotherapy spills, and handling patient excreta. During the course of patient treatment, healthcare professionals may inadvertently be exposed to these agents, thus placing themselves at risk.

Experimental evidence indicates that at least nine commonly used chemotherapeutic agents for which there is no known safe level of exposure may pose carcinogenic risks to humans. This evidence is based on epidemiological research that associates secondary tumors in cancer patients treated with these drugs. Experimental animal studies have also identified carcinogenic and teratogenic effects associated with exposure to several antineoplastic agents, including the alkylating agents and antimetabolites.

Which anticancer drugs cause cancer?

The International Agency for Research on Cancer (IARC) in Lyon, France, has evaluated 900

**KEY POINTS**

- Concern has been growing regarding the safety of healthcare workers who handle chemotherapy drugs.
- Probable exposure routes include dermal absorption, ingestion, and inhalation.
- Acute symptoms in nursing staff have been identified, including nausea, vomiting, headaches, dizziness, hair loss, and liver damage.
- Exposure poses a significant risk to reproductive health among female staff members, including infertility, preterm deliveries, spontaneous abortions, fetal abnormalities, and small-for-gestational-age births.
- A significant increase risk for leukemia has been noted among healthcare workers.
- Implementing safety recommendations can prevent or reduce exposure and minimize potential adverse effects.
agents for their potential to cause cancer in humans. Below is the list of drugs used to treat cancer patients that have made it onto the IARC’s list of carcinogens, plus possible and probable carcinogens (Table 1).

Conceptually, an occupational exposure to hazardous chemotherapeutic agents is defined as the degree of internal exposure to hazardous antineoplastic agents after a healthcare worker’s inadvertent occupational contact with chemotherapy drugs during the preparation, administration, and/or disposal process. The degree of internal antineoplastic chemotherapeutic exposure reflects the quantity of drug uptake, the metabolism of the drug in the body, and evidence of cellular manipulation after an accidental exposure with cytotoxic agents during the handling process.

The conceptual framework associated with occupational exposure is based on the epidemiological triad of host, agent, and environment. It is hypothesized that the adverse health effects identified in oncology healthcare workers are a product of an interaction between the person at risk (host), an exposure to antineoplastic chemotherapeutic (agent), and the environment (handling practices). Each component of this theoretical triad may affect the validity and reliability of tools that attempt to quantify exposure to these agents. Individual variations in the host may affect the absorption as well as the sensitivity and specificity of the measurement method. Such variations are associated with the subjects’ genetic makeup; percentage of body fat; gender; social, religious, and cultural norms; and nutritional status and lifestyle habits.

The metabolism of the chemotherapeutic agent, its pharmacokinetics, the temporal relationship between exposure and testing, and the agent’s physiological toxicity may significantly affect the validity and reliability of the outcome data. Lastly, the handling practices of the subjects, such as the use of personal protective equipment and biological safety cabinets, may affect the quantity of internal absorption of these substances.

### TABLE 1

**Potentially carcinogenic chemotherapeutic agents**

<table>
<thead>
<tr>
<th>Carcinogenic to humans</th>
<th>Probable carcinogens</th>
<th>Possible carcinogens</th>
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<tbody>
<tr>
<td>Azathioprine</td>
<td>Azacitidine</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Carmustine (BiCNU)</td>
<td>Dacarbazine</td>
</tr>
<tr>
<td>Chlorambucil (Leukeran)</td>
<td>Cisplatin</td>
<td>Daunorubicin</td>
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<tr>
<td>Cyclophosphamide</td>
<td>Doxorubicin</td>
<td>Mitomycin</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Etoposide</td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td>Semustine*</td>
<td>Lomustine (CCNU, CeeNU)</td>
<td>Streptozocin (Zanosar)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Mechlorethamine</td>
<td></td>
</tr>
<tr>
<td>Thiopeta</td>
<td>(nitrogen mustard)</td>
<td></td>
</tr>
<tr>
<td>Treosulfan*</td>
<td>Procarbazine (Matulane)</td>
<td></td>
</tr>
<tr>
<td>MOPP† and other regimens containing alkylating agents</td>
<td>Teniposide (Yumon)</td>
<td></td>
</tr>
</tbody>
</table>

* Not approved in the US  † MOPP = mechlorethamine, vincristine, procarbazine, and prednisone

For details, visit the IARC Web site: www-iarc.fr/monoeval/grlist.html

Reproductive and developmental effects

In addition to acute adverse effects, several studies have indicated an association of hazardous drug exposure with long-term adverse effects. Exposure to chemotherapeutic agents poses a significant risk to female reproductive health. The literature reports the incidence of such reproductive deficits as infertility, spontaneous abortions, fetal abnormalities, and menstrual-cycle abnormalities.

Among nurses and pharmacists who reported occupational chemotherapy exposure, a cross-sectional self-reported survey found an increased prevalence of infertility. Among women, there was a significant increase in reported cases of infertility among nurses handling chemotherapy (odds ratio [OR] = 1.5; 95% confidence interval [CI] = 1.1–2.0), regardless of a history of exposure with long-term adverse effects. This symptom was associated with the employee’s duration of work exposure and the volume of handling.

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exposure to cytotoxic agents. The researchers found that women exposed to antineoplastic drugs during the first trimester of pregnancy were more than twice as likely to experience fetal loss as women who were not exposed and carried their pregnancies to full term. Stucker et al showed a relative risk of 1.7 (95% CI = 1.0–2.8) among nurses who, on average, prepared and administered 18 chemotherapy infusions per week without personal protective equipment. Valanis and colleagues reported that spontaneous abortions were associated with chemotherapy handling during pregnancy (OR = 1.5; 95% CI = 1.2–1.8).

Several additional negative reproductive outcomes have been noted following cytotoxic drug exposure. Savitz et al found that women who were occupationally exposed to antineoplastic agents reported an increased risk of preterm deliveries and small-for-gestational-age births. This study did not delineate, however, whether the noxious drug exposure was preconception or during pregnancy. The effects of potential chromosomal aberrations are reflected in increased incidences of miscarriages and malformations in offspring. Two studies of nurses occupationally exposed to cytotoxic drugs showed relative risks for miscarriages of 2.30 and 1.70, respectively. Hemminki et al found an OR of 4.70 for malformations in the offspring of nurses handling cytotoxic agents.

Genetic effects

The genetic effects associated with exposure to a broad spectrum of antineoplastic agents have been studied extensively. Genotoxic activity of some antineoplastic agents in humans has been noted in both patients treated with the agents as well as those healthcare personnel administering the agents. The incidence of DNA single-strand breaks in peripheral mononuclear blood cells was 50% higher in nurses not utilizing recommended safety precautions. This finding is significant since other major carcinogens, such as exposure to smoke, present with the identical DNA strand breaks. Chromosomal aberrations were also noted in nurses and physicians handling antineoplastic drugs. The length of handling exposure was the predominant factor that correlated with the degree of chromosomal damage.

Cancer development

An increased risk of malignancy, predominately leukemia, among healthcare workers in general has been previously reported. Blair and colleagues reported that hospital workers were 2.9 times (95% CI = 1.4–6.9) more likely to develop acute myelogenous leukemia than non-hospital workers in the Iowa area.

The literature regarding the risk of cancer among healthcare personnel who handle antineoplastic drugs is limited and has focused predominantly on leukemia. Skov et al reported a nonsignificant increased risk of developing leukemia among physicians who handled chemotherapy (relative risk [RR] = 2.85; 95% CI = 0.51–16.02). A significant increased risk for leukemia was noted among oncology nurses who handled chemotherapy agents (RR = 10.65; 95% CI = 1.29–38.5). Nevertheless, there is a wealth of information in the literature regarding occupational chemotherapy exposure and elevated levels of nonspecific markers for carcinogen exposure, such as sister chromatid exchanges and chromosomal aberrations.

Sister chromatid exchanges are symmetrical rearrangements of DNA within chromosomal structures in T lymphocytes; they were noted after exposure to a known carcinogen.

Conclusion

Occupational exposure from hazardous drugs may pose a significant risk to healthcare workers. Since the mid-1980s, several organizations have published recommended hazardous drug handling guidelines. Most recently, the National Institute of Safety and Health (NIOSH) published an alert that presents the most updated recommendations for hazardous drug handling. Implementing these recommendations may prevent or reduce the inadvertent exposure to these drugs, thus minimizing the potential adverse health effects associated with their handling.

For more on implementing the NIOSH guidelines, see the following article, “Developing a hazardous drug safe-handling program,” by Martha Polovich, MN, RN, AOCN.

References

3. Crudi C, Stephen B, Maier P. Possible occupational hazards associated with the preparation, administration of antineoplastic agents. NITA 1982;5:264–266.


