Antineoplastic Drugs:

hazardous, handle with care

While antineoplastic/chemotherapy drugs have played an important role in cancer treatment, some cancer patients can develop secondary malignancies such as leukemia and bladder cancer. Research, perhaps best summarized by the U.S. National Institute of Occupational Safety and Health (NIOSH) reports some of these secondary cancers have been linked to certain classes of chemotherapy drugs such as "alkylating agents". So if patients receiving chemotherapy are at increased risk of developing secondary cancers, what is the risk to health care workers who prepare and administer these agents?

Researcher Christopher Friese says, "Any unintentional exposure to the skin or eyes [of antineoplastic agents] could be just as dangerous as a needlestick." Unlike needlesticks where a specific virus is involved and preventive treatments can be given, it's more difficult to link chemotherapy exposure to a direct health effect. This makes it more difficult for health care systems to respond to these incidents.

Chemotherapy drugs are not restricted to just adult and paediatric oncology suites of the hospital, but are also found in operating rooms, and follow the patient to the post anesthesia room and the inpatient units. The adverse health risks are also present in transplant units, neurology units, and outpatient urology. As such, nurses, porters, pharmacists, and support workers are just some of the individuals who may be exposed to antineoplastic drugs. Also at issue is that antineoplastic tablets are used out in the communities, in long-term care facilities and in the home.

What are antineoplastic drugs?

Antineoplastic drugs are part of a larger group called "hazardous drugs". Hazardous drugs are drugs that pose a potential health risk to health care workers who may be exposed during preparation or administration. Most drugs are considered "hazardous" if they are cytotoxic (i.e. inhibit or prevent cell function) like "antineoplastic", or "chemotherapeutic" agents used to treat cancer. Currently the term "hazardous" is preferred over "chemotherapy" or "antineoplastic" because it is more inclusive of all drugs that present a risk. These include biologic, antiviral, and immunosuppressive agents, as well as drugs from other classes. Thalidomide, interferon alpha, conjugated estrogens, and gancyclovir (an antiviral agent) are examples of medications that are also potentially harmful.

For purposes of this publication emphasis will be placed on antineoplastic drugs.

Antineoplastic drugs have been used in the treatment of cancer for more than 50 years. Poisonous by design, these powerful drugs are used clinically to:

- destroy or control the growth or spread of cancer cells,
- "cure" the cancer or put it "in remission",
- "ease symptoms" such as pain or pressure from a tumour when a cure is not possible and the outlook is poor (palliative care).

Antineoplastic drugs work by interfering with DNA replication. Because cancer cells are rapidly dividing they are rapidly synthesizing new DNA — and when this DNA is damaged by the hazardous agent the cell will die. Unfortunately, anticancer agents are non-selective in their actions and also disrupt the growth and function of healthy (non-cancerous) cells causing adverse health effects in the patients who receive them and the workers who administer them.

What are the health effects?

According to NIOSH virtually all antineoplastic drugs have side effects associated with patient use. Workers who handle antineoplastic drugs may be at risk of suffering the same effects as their patients without reaping any of the benefits.

The likelihood of an adverse event resulting from occupational exposure to antineoplastic drugs can vary with the dose and frequency of the exposure, and the extent to which the drug is absorbed into the body. Also important is whether or not safe work practices have been followed and in the case of a pregnant health care worker, the point during a pregnancy and/or fetal development at which the exposure occurs. Exposure to even very small concentrations of certain drugs may be hazardous for all workers who handle them. In these cases there are no safe limits.

Acute or Short-Term Effects: Nurses, pharmacists and pharmacy technicians routinely exposed to antineoplastic drugs in the workplace may experience acute or

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short-term symptoms such as: nausea, sore throat, chronic cough, infections, mouth and nasal sores, dizziness, headaches, skin and eye irritation, contact dermatitis, allergic asthma, vomiting, diarrhoea, abdominal pain, or hair loss/thinning.

Long-Term or Chronic Effects: There are a number of long-term or chronic effects that have been identified in health care workers working with or near these potent drugs. These health effects include: liver and kidney damage; damage to the bone marrow; damage to the lungs and heart; infertility (temporary and permanent); effects on reproduction and the developing fetus in pregnant women; learning disabilities in offspring, hearing impairment; and cancer.

Reproductive studies on health care workers have shown an increase in fetal abnormalities, fetal loss, and fertility impairment resulting from occupational exposure to antineoplastic drugs.

Cancer: Antineoplastic drugs were first introduced in the 1940s. By the 1970s the carcinogenicity of several antineoplastic drugs was well established in animal studies. Also during this period a number of researchers linked the therapeutic use of alkylating agents in humans to subsequent leukemias and other cancers. A review of 19 published epidemiological studies of nurses, conducted between 1983 and 2001, concluded that nurses may be at increased risk of breast cancer and leukemia related to their work.

In a 1990 Danish study, a significantly increased risk of leukemia has been reported among oncology nurses for the period of 1943 to 1987. The same researchers found an increased, but not significant, risk of leukemia in physicians employed for at least six months in a department where patients were treated with antineoplastic drugs.

Other malignancies include Non-Hodgkin lymphoma, bladder, and liver cancers.

IARC: The International Agency for Research on Cancer (IARC) in France has evaluated and classified several antineoplastic drugs as Group 1 (human carcinogens). These drugs are *Azathioprine, Busulfan, Chlorambucil, Cyclophosphamide, Melphalan, Tamoxifen, Thiotepa, Treosulfan, MOPP (Mustargen, Oncovin, Procarbazine, and Prednisone)* and a combination of *Etoposide, Cisplatin*, and *Bleomycin (ECB)*. Other antineoplastic drugs have been classified as *probable* or *possible* human carcinogens.

Who is at risk?

CAREX, a Canadian multi-institution cancer surveillance research project, estimates that in 2012, approximately 58,000 Canadians will be occupationally exposed to antineoplastic agents. Almost three-quarters of these will be women. Although significant exposures can occur during manufacturing, health care workers, especially nurses and pharmacists are the most commonly exposed.

In 2009, as many as 15,800 nurses were exposed to hazardous drugs by caring for patients receiving the drugs; working with the drugs directly; or being in the same room where the drugs are administered. More than one third of them worked in Ontario.

Workers at risk also include other therapists who deal directly with patients receiving chemotherapy; as well as custodial, laundry, waste, clerical, teaching and dietary workers with responsibilities in the health care environment.

How are workers exposed?

In a recent study conducted in 2011, researchers from the University of Michigan reported that nearly 17 per cent of nurses who work in outpatient chemotherapy infusion centres reported being exposed on their skin or eyes to the antineoplastic drugs they deliver.

Occupational exposure to antineoplastic drugs occurs directly and non-directly through skin absorption, ingestion, inhalation, or accidental injection. Both clinical and non-clinical workers may be exposed to antineoplastic drugs when they create aerosols; generate dust; clean up spills; or touch contaminated work surfaces during the preparation, administration, or disposal of these toxic agents.

Activities/procedures that may result in exposure include: administering antineoplastic drugs by intramuscular, subcutaneous or intravenous (IV) routes; counting out individual, uncoated oral doses and tablets from multi-dose bottles; crushing tablets to make oral liquid doses; touching the outside of contaminated drug vials, work surfaces, and floors; handling contaminated body fluids or contaminated clothing, dressings, linens and other materials; and handling contaminated wastes generated at any step of the preparation or administration process. Other activities include: removing and disposing of personal protective equipment (PPE) after handling antineoplastic drugs or waste; and eating food or beverages that are prepared, stored, or consumed in contaminated work areas (such as a refrigerator). Exposure can also occur fro unexpected leaks from malfunctioning chemotherapy delivery equipment.

While the majority of antineoplastic drug are stored, prepared and administered in limited number of locations (i.e., oncolog pharmacy, care units, outpatient clinics etc.), the numbers and types of work environments containing antineoplastic drugs are expanding. Increasingly, antineoplastic drugs are used in the operating rooms (for bladder cancer). An chemo drugs such as *Cyclophosphamide, Methotrexate* and *Azathioprine* are used to treat non-malignant diseases such as arthritis. The workers who work in these areas are often overlooked as being at ris for exposure to these toxic drugs.

What is the law?

Although there is no mention of antineoplastic drugs in the *Occupational Health and Safety Act*, employers are required to take every reasonable precaution to protect workers from exposure to hazardous chemicals and biological agents. Antineoplastic drugs are specifically addressed in *Ontario Regulati 67/93 Health Care and Residential Faciliti*

Ontario Regulation 67/93 Health Care ar Residential Facilities

Section 97 (1) requires the employer, in consultation with the joint health and safe committee (JHSC) or health and safety representative, if any, "to develop, establi and put into effect written measures and procedures to protect workers who may be exposed to antineoplastic agents or to material or equipment contaminated with antineoplastic agents."

These measures and procedures must include:

a) procedures for storing, preparing, handling, using, transporting, and disposing of antineoplastic agents an contaminated material;

b) emergency procedures to be followec if a worker is exposed to antineoplast drugs;

c) procedures for maintenance and disposal of contaminated equipment;

d) measures for the use of engineering controls, work practices, hygiene practices and facilities, or appropriate personal protective equipment; and

e) measures for the use of an appropriate biological safety cabinet to prepare antineoplastic agents.

Employers (covered by the regulation) must also, in consultation with the JHSC and health and safety representative, provide training and education programs in these measures and procedures to workers who may be exposed to antineoplastic drugs or contaminated materials or equipment.

What about control measures?

In the absence of more specific regulations many organizations and government agencies have developed guidelines and standards of practice for health care workers, pharmacists and others who come into contact with antineoplastic drugs while caring for their patients who need them.

NIOSH 2004 Alert: In 2004, NIOSH developed a revised alert called *NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings* which has been adopted by organizations such as the American Society of Health-System Pharmacists (ASHP), Oncology Nursing Society (ONS), Canadian Association of Pharmacy Oncology (CAPhO) and many other government and professional associations here in Ontario and worldwide.

NIOSH recently updated the *List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings in 2010*. Closer to home, the Ontario Nursing Society has published the *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice* (2001).

As discussed above, the risk of contamination with antineoplastic drugs exists in the preparation, administration and disposal of these toxic agents. Therefore, it is critical that JHSCs or health and safety representatives consider the following protective measures to reduce worker exposures.

Preparation of Antineoplastic Drugs

NIOSH (2004) recommends the following controls when preparing antineoplastic drugs:

- ✓ Use a Class II or III biological safety cabinet (BSC) or an isolator designed to protect workers by containing aerosols generated during drug preparation. All types of ventilated safety cabinets should have a HEPA filter to exhaust 100 per cent of filtered air to the outside.
- ✓ Do not use a ventilated safety cabinet that re-circulates air inside the cabinet or exhausts air back into the room environment unless the antineoplastic drug(s) in use will not evaporate while they are being handled or after they are captured by the HEPA filter.
- ✓ Train all workers who use BSCs to use work practices established for their particular equipment.
- ✓ Workers must wear proper gloves and gowns when opening drug packaging; handling vials or finished products; labelling hazardous drug containers; or disposing of waste. Wear double gloves and protective gowns while constituting and admixing drugs.
- ✓ Use closed-system transfer devices (CSTD), glove-bags, and needle-less systems when transferring hazardous drugs from primary packaging (such as vials) to dosing equipment (such as infusion bags, bottles, or pumps). Closed systems limit the potential for generating aerosols and exposing workers to sharps.
- ✓ CSTDs are not an acceptable substitute for a ventilated cabinet and should be used within a Class II BSC for optimum results. Ventilation and biosafety cabinets should be maintained and evaluated for proper performance according to manufacturer's instructions.

Closed System Transfer Devices

There are a variety of closed system transfer devices available commercially—some are more effective than others. When purchasing a CSTD be sure that it meets NIOSH's criteria for a closed system device.

In 2008, research by J. A. Jorgenson (University of Utah) found that PhaSeal was an effective device. Out of five devices tested PhaSeal was the only one that maintained a dry connection throughout the testing meeting NIOSH criteria for a CSTD. PhaSeal features double membranes and an expansion chamber; includes a connector lock to ensure a sealed connection between the injector and the patient's intravenous line; an infusion set with a built-in connector; and an infusion adaptor with an inline spike to connect the bag to the external intravenous set. Other studies have also found PhaSeal effective.

Administration and Disposal of Antineoplastic Drugs

When administering and disposing of hazardous drugs:

- ⇨ Use protective medical devices (such as needle-less and closed-systems) and techniques (such as priming of IV tubing by pharmacy personnel inside a ventilated cabinet or priming in-line with non-drug solutions).
- ⇨ Wear PPE (including double gloves, goggles and protective gowns) for all activities associated with drug administration — opening the outer bag, assembling the delivery system, delivering the drug to the patient and disposing of all equipment used to administer drugs.
- ⇨ Infusion sets and pumps which should have Luer-lock fittings should be observed for leakage during use. A plastic-backed absorbent pad should be placed under the tubing during administration to catch any leakage.
- ⇨ Attach drug administration sets to the IV bag and prime them before adding the drug to the bag.
- ⇨ Use routine practices and additional precautions in accordance with advice from Public Health Ontario to prevent contact with blood or other potentially contaminated or infectious body fluids.
- ⇨ Remove the IV bag and tubing intact when possible.
- ⇨ Use and dispose of sharps carefully. Place disposable items directly in a *chemotherapy* waste container and close the lid.
- ⇨ Avoid touching equipment (e.g., infusion pumps, computer keyboards, telephones) when wearing gloves used to handle hazardous drugs.
- ⇨ Clean countertops and other surfaces in the work area after completion of hazardous drug handling.
- ⇨ Remove outer gloves and gowns, and bag them for disposal in the *chemotherapy* waste container at the site of drug administration.
- ⇨ Double-bag the chemotherapy waste before removing the inner gloves. Consider double-bagging all contaminated equipment.
- ⇨ Wash hands with soap and water before leaving the drug administration site.

Personal Protective Equipment (PPE)

On its own, personal protective equipment is the least desirable of control measures. However, when it comes to exposure to hazardous drugs proper PPE is effective when used in conjunction with other control measures.

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Gloves: Only disposable, powder-free gloves that have been properly tested for use with hazardous drugs (e.g., nitrile, polyurethane, and neoprene) should be used. Gloves should be inspected for visible defects prior to use and double gloves should be worn for all handling activities such as preparation, administration, and handling of contaminated waste. When applying double gloves, workers should place the inner glove under the gown and the outer glove over the cuff.

Gloves should be changed every 30 minutes or immediately if damaged or contaminated and not reused. Workers should wash their hands with soap and water before donning protective gloves and immediately after removal.

Gowns: Also effective are disposable, lint-free, low permeability fabric (e.g., polyethylene-coated materials) gowns. These protective garments should have a solid front and a back closure, long sleeves and elastic or knit closed cuffs.

Workers should discard the gown: if it becomes visibly contaminated; before leaving the area where drug is handled; and after handling the drug. A frequently overlooked standard is the need to use a new gown for each drug administration, as gowns are for single use only and should not be reapplied throughout the shift.

Mask: Additional protection should include a fluid-resistant mask and face shield when the possibility of eye, mouth, or nasal splashing exists (such as during a bladder instillation of hazardous drugs). Goggles protect the eyes but not the face against spraying. Surgical masks do not provide respiratory protection and should not be relied upon for protection against aerosolized powders or liquids such as during drug preparation.

Respiratory Protection: Respiratory protection is necessary when drug aerosols are present, such as when administering aerosolized hazardous drugs or when cleaning spills. For most activities requiring respiratory protection, Oncology Nursing Society (ONS) recommends a fit-tested NIOSH-approved N95 respirator which is sufficient to protect against airborne particles. A self-contained breathing apparatus is appropriate when there is risk of aerosol generation in a space with no engineering controls (e.g., when cleaning out the biological safety cabinet, cleaning up spills, or other emergency situations).

Safe Handling Program: Each facility should develop policies and procedures for the safe handling of hazardous drugs. This program must be developed with input from all affected departments including the joint health and safety committee(s). A key element of this safety program is access to up-to-date Material Safety Data Sheets (MSDS).

A safe handling program should include the following:

- Identification and assessment of all hazardous drugs used in the facility and methods for updating the list.
- Policies and procedures for the safe storage, transport, administration and disposal of hazardous agents.
- Policy requiring all workers handling antineoplastic drugs to wear proper PPE.
- Mandatory training for all workers, and supervisors who work with, or may be exposed to, antineoplastic drugs. Training should be hands-on and delivered during orientation and at least annually thereafter. Training should cover potential health risks of antineoplastic drugs, containment systems, sources of information, administration and disposal, appropriate use and care of PPE, and procedures for handling spills. There should also be some awareness train for JHSC members.
- Clear policies for workers regarding reproductive risks including the offer of alternative duties for pregnant or breastfeeding workers, as well as reasonable scheduling patterns to reduce the potential for overexposur
- Policies prohibiting eating, drinking, smoking, chewing gum or tobacco, applying cosmetics, and storing food in areas (e.g., refrigerator) where antineoplastic drugs are used/stored

Handling of Spills

Antineoplastic drug spills should be managed according to the established, written policies and procedures for each workplace. Assure written policies and procedures address PPE required for varic spill sizes; possible spreading of material; restricted access to hazardous drug spills; and signs to be posted. Cleanup of a large spill should only be handled by workers w are trained in handling hazardous materia This includes housekeeping and cleaning staff who should also receive training. Spi procedures regarding containment, cleani and disposal need to be defined and followed carefully.

EDITOR'S NOTE: *For more comprehensive information on handling antineoplastic drug spills contact the Workers Health & Safety Centre. There are also many excellent resources on the safe handling of hazardous/antineoplastic drugs. A very comprehensive guide is the Safe Handling of Hazardous Drugs (Second Edition) published by the Oncology Nursing Society (ONS), 2011, edited by Martha Polovich.*

