Safe Handling of Parenteral Cytotoxics: Recommendations for Ontario

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Abstract

Purpose: To develop a set of recommendations for the safe handling of parenteral cytotoxics in health care facilities in Ontario, Canada.

Methods: Systematic reviews were conducted to assemble evidence on risks to health care staff who prepare or administer cytotoxic drugs for cancer care and on closed systems for handling these drugs. Recent guidelines on safe handling of hazardous drugs were also reviewed. A multidisciplinary expert panel used an ethical framework to interpret this evidence and develop a set of recommendations to guide oncology practice in Ontario. Practitioners were surveyed and asked to provide input for the final set of recommendations.

Results: Available evidence on risks associated with handling

cytotoxic drugs is of poor quality, but it suggests that health care workers exposed to cytotoxic agents may be at increased risk for miscarriages. There is general agreement across guideline development groups in North America, Europe, and Australia concerning recommendations related to policies and procedures for handling cytotoxic drugs, use of personal protective equipment, and standards for ventilated cabinets, syringes and intravenous sets, transport and labeling, and education and training of staff. Limited evidence from poor-quality studies suggests that closed systems may reduce surface contamination with hazardous drugs during preparation.

Conclusion: A set of recommendations was formulated by the expert panel and approved by practitioners surveyed across Ontario.

Introduction

Chemotherapy has an important role in cancer treatment; it is potentially curative when used as adjuvant therapy in patients with early-stage tumors and offers effective palliation in patients with metastatic disease. However, some patients who have been cured of cancer develop secondary malignancies believed to be linked to exposure to their initial chemotherapy regimens.¹⁻⁵ If patients receiving potentially curative chemotherapy are at increased risk of developing secondary cancers, what is the risk to health care workers who prepare and administer these agents? Nurses, pharmacists, pharmacy technicians, porters who deliver cancer drugs to chemotherapy units, and physicians may be exposed to cytotoxic agents during care of patients with cancer. In addition to being at risk for exposure-related cancers, these individuals might develop acute toxic effects after accidental spills of cytotoxic agents. In female health care workers who become pregnant, there are also the potential hazards of spontaneous abortions, stillbirths, and teratogenic effects on unborn fetuses. Occupational exposure to cytotoxic drugs was recognized as a potential hazard for health care workers in the 1970s, when Falck et al,⁶ studying the mutagenicity of urine samples, first demonstrated potential risk for nurses handling these drugs. Subsequent examinations of the workplace documented detectable levels of drugs in airborne samples and on work surfaces,^{7,8} confirming that exposure is possible even in the absence of

obvious direct contact. No long-term adverse effects of occupational exposure were conclusively demonstrated, but potential risk was deemed serious enough to warrant the issuing of several drug-handling guidelines during the 1980s and 1990s.⁹⁻²⁰ These guidelines promoted control of exposure through implementation of stringent procedures, use of specialized equipment and personal protective equipment, and education of those handling these drugs or at risk for exposure. As a result, many institutions introduced and implemented policies and procedures designed to minimize occupational exposure and consequent risks associated with handling cytotoxic drugs. Nevertheless, health hazards may still exist for hospital staff, as suggested by environmental contamination studies that have demonstrated measurable levels of contamination in the workplace despite the standards of practice in place.²¹ Detectable levels of cytotoxic drugs have been reported in the urine of pharmacists, pharmacy technicians, nurses, and workers in drug manufacturing plants.²²

In 2003, Cancer Care Ontario (Toronto, Canada) formed a task force to examine evidence on adverse effects among health care workers from exposure to cytotoxic agents. Results of the systematic review and meta-analysis conducted by this task force were published in 2005.²³ Subsequently, an expert panel was assembled to review evidence on adverse effects and on closed handling systems for handling cytotoxics, as well as avail-

able guidelines on this topic, and to develop recommendations for use in Ontario. A full report on the recommendations and development process can be found at <http://www.cancercare.on.ca/pdf/pebccytos.pdf>.

Methods

An expert panel comprising pharmacists, nurses, an ethicist, an oncologist, and an occupational health and safety manager interpreted available evidence, reviewed recommendations made by similar groups in other countries, drafted recommendations, and obtained feedback from practitioners across Ontario.

Initial evidence came from a systematic review of evidence on risks to health care workers from handling cytotoxic drugs; methods for this review have been published elsewhere.²³ The expert panel updated the review before drafting recommendations. The updated review included literature published in full reports or meeting abstracts before July 2006 and addressed questions regarding whether health care workers who work with cytotoxic drugs are at increased risk for cancer, teratogenic births, stillbirths, miscarriages, acute toxic effects (skin rash, nausea, and so on), or having children with developmental delays, compared with a control group of unexposed health care workers.

The panel also conducted two additional systematic reviews: one of existing guidelines and one of closed systems. The National Guideline Clearinghouse database (<http://www.guideline.gov>), CMA Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>), and MEDLINE (Ovid), CINAHL (Ovid), and EMBASE (Ovid) databases were searched in January 2006 for guidelines published in English after January 2003. Google (<http://www.google.ca>) was also used to search the Web for documents that included the text “safe handling” or “hazardous drugs.” For the review of closed systems, MEDLINE (Ovid), CINAHL (Ovid), EMBASE (Ovid), and HealthStar (Ovid) databases and the Cochrane Central Register of Controlled Trials were searched from inception to July 2006. Proceedings of the annual meetings of ASCO from 2001 to 2005, the American Society of Hematology for 2005, the Oncology Nursing Society from 2003 to 2006, and the Canadian Society of Hospital Pharmacists from 2005 to 2006 were searched for studies published in abstract form but not yet available as full reports. Reference lists of eligible studies and published reviews were scanned to identify additional articles. All study designs were eligible for inclusion in the review.

Methods developed and refined by the Program in Evidence-Based Care (PEBC) of Cancer Care Ontario were used to review evidence and develop recommendations.^{24,25} After the review, the expert panel addressed the question, “What precautions should be taken in the workplace to minimize risk of adverse effects among hospital and clinic staff who may be exposed to cytotoxic drugs?” In addition to published evidence and guidelines, the expert panel used an ethical framework invoking the principles listed in Table 1 to reach consensus on a

Table 1. Ethical Framework

Principle
Recognition that there is a duty to provide care, even if providing care is associated with risk, and that trained professionals are the best people to provide this care
Appropriate recognition and support of those who take risks for others
As far as reasonably possible, mitigation of risks for those who take risks to help others
Alertness to the need for extra caution and safety measures, and responsiveness to the reported needs and concerns of staff and experts
Access to and appropriate use of safety measures and equipment
Timely implementation of safety improvements, and encouragement of research that will improve safety measures
Equal opportunity for avoiding risks in reasonable situations (eg, pregnancy)
Availability of ongoing education and updates
Duty to provide care and treatment in the event of harm caused by cytotoxic agents

set of recommendations. This framework was developed on the basis of existing proposals for other areas of health care delivery,²⁶ professional values of panel members, and values inherent in studies and guidelines found in the systematic review.

A detailed report that included a full description of the systematic review, detailed recommendations, and the rationale for the recommendations was reviewed and approved by the PEBC Report Approval Panel, which has expertise in clinical and methodologic issues. The report was sent to 111 oncology pharmacists and nurses in Ontario for review and feedback. The questionnaire included items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and asked whether the draft recommendations should be approved. The expert panel reviewed results of the survey and modified some of its recommendations.

Results

Evidence on Risks to Health Care Workers

Our systematic review of 15 retrospective studies (one cohort study, four case-control studies, and 10 surveys) that compared health care workers exposed to cytotoxic agents with those who were not exposed found that health care workers exposed to cytotoxic agents may be at increased risk for miscarriages, but the quality of available evidence is poor.^{23,27} Meta-analysis of data from five retrospective studies detected an excess of spontaneous abortions among those exposed to cytotoxic drugs (pooled odds ratio [OR], 1.46; 95% CI, 1.11 to 1.92). The association between workplace exposure to cytotoxics and congenital malformations, ectopic pregnancies, and stillbirths was unclear. Meta-analysis of data from four studies failed to detect a statistically significant association for congenital malformations (pooled OR, 1.64; 95% CI, 0.91 to

2.94). Two studies failed to detect associations with ectopic pregnancies and stillbirths, respectively. There was insufficient evidence in published studies to determine if health care workers exposed to cytotoxic drugs are at increased risk for acute toxic effects or cancer or if their children are at increased risk for learning disabilities.

Existing Guidelines

Eight guidelines on safe handling of hazardous drugs have been published since 2003²⁸⁻³⁵ in the United States, Australia, the United Kingdom, and Germany. The most recent guidelines, published in June 2006, were developed by the American Society of Health System Pharmacists (ASHP; Bethesda, MD).²⁸ None of the guidelines were evidence based (ie, based on a systematic review of evidence), but the ASHP guidelines provided narrative summaries of evidence related to each recommendation. Guidelines by the ASHP and Australian guidelines by WorkSafe Victoria (Melbourne, Australia) covered all areas of interest to the expert panel, and other guidelines included recommendations related to most of these issues. There was general agreement across guideline development groups that appropriate precautions related to policies and procedures, personal protective equipment, ventilated cabinets, syringes and intravenous sets, transport and labeling, and education and training should be employed.

Evidence on Closed Systems

Although seven studies of closed systems for handling hazardous drugs were identified, they provided little evidence to inform decisions about effectiveness of this technology to reduce exposure among health care workers preparing or administering cytotoxic drugs.³⁶⁻⁴² All studies measured surface contamination, and two also measured cytotoxics in urine of pharmacy staff and nurses. The studies were descriptive in nature. Although five studies compared open and closed systems, they were not designed to evaluate differences between groups. None of the studies were randomized, and none included statistical analyses of results. Nevertheless, the observed results suggest potential for contamination to be reduced with closed systems and point to a need to test this hypothesis in well-designed studies.

Recommendations

The final recommendations, which incorporate feedback from the PEBC Report Approval Panel and practitioner survey, are listed in Table 2. The target population for the recommendations includes any employee of a health care facility in Ontario who may be involved in handling cytotoxic drugs or related waste or bodily fluids from patients undergoing treatment with cytotoxic drugs. This generally includes staff in the following departments: medicine, nursing, pharmacy, housekeeping, environmental services, transportation and portering, materials management, clinical laboratory, research, and clinical trials. The recommendations are intended to apply to all health care institutions in Ontario that administer parenteral cytotoxic drugs.

Discussion

The expert panel accepted that the link between exposure of health care workers to cytotoxic drugs and adverse outcomes is biologically plausible. Although the quality of evidence is weak, it does indicate that health care workers exposed to cytotoxic agents may be at increased risk for miscarriages. Evidence related to other risks associated with workplace exposure to cytotoxic drugs is insufficient to reach any firm conclusions. The expert panel concluded that available evidence raises concerns about potential for harm to health care staff working with cytotoxic drugs. The panel agreed that recommendations to address these risks were needed for Ontario and that emphasis should be placed on minimizing exposure to cytotoxic drugs for all staff at all times. The recommendations for Ontario were designed to provide guidance to institutions and individuals without being overly prescriptive about details of implementation and to inform institutions as they assess the adequacy of their facilities, policies, and procedures.

The recommendations draw on the work of guideline developers in North America, Europe, and Australia related to policies and procedures, personal protective equipment, ventilated cabinets, syringes and intravenous sets, transport and labeling, and education and training. To our knowledge, no studies have examined effectiveness of these precautions in reducing rates of cancer, adverse reproductive outcomes, or acute adverse effects associated with exposure to cytotoxic drugs among health care workers, but there is evidence that some types of gloves and gowns offer protection against penetration and permeation by hazardous drugs. Although there is wide acceptance of ideal standards for these practices, implementation is variable and often less than ideal.

There is less agreement across guidelines with respect to closed systems, pregnancy, and medical surveillance of health care workers. Closed systems are a new, expensive, and unproven technology. Their use was not standard practice in Ontario when these recommendations were developed. Although most guideline developers acknowledged that there is evidence of adverse reproductive outcomes among health care workers handling cytotoxics, there is variation among guidelines in the strength of recommendations for protecting pregnant workers from exposure. After considerable discussion, the Ontario panel recommended that employees be informed of the risks and offered alternative duties. Routine medical surveillance for all workers was not recommended, because biologic monitoring for occupational diseases requires an identified hazard and accepted and detectable clinical outcome that can be reliably identified by clinical tests. These elements are lacking in the current research on health effects of cytotoxic drugs among exposed health care workers. There are no exposure limits set for cytotoxic drugs and no standards for interpretation of test results of exposed health care workers to enable meaningful interpretation or action on the basis of biologic monitoring results.

Table 2. Key Recommendations

Topic	Recommendation
Policies and procedures	<p>Written policies and procedures for handling cytotoxic drugs, related waste, and body fluid disposal are needed in each setting; development must be collaborative and consultative, involving departments such as medicine, nursing, pharmacy, housekeeping, environmental services, transportation and portering, materials management, clinical laboratory, research, and clinical trials as well as employee health, risk management, industrial hygiene, and safety officers and joint health and safety committees</p> <p>Policies and procedures must be readily accessible and focus on training for all relevant employees</p> <p>Policies and procedures must be reviewed and updated annually, in consultation with appropriate stakeholders</p>
Personal protective equipment	<p>Personal protective equipment is provided by health care facility for all staff handling cytotoxic drugs</p> <p>Staff are required to wear personal protective equipment in accordance with written policies</p> <p>Personal protective equipment must be used when preparing or administering cytotoxic drugs, handling waste, or cleaning up spills and must include at least:</p> <ul style="list-style-type: none"> Gloves meeting ASTM D6978-05 standards Disposable gown (made of appropriate materials designated protective against cytotoxic drugs) or reusable gown designed to be nonpermeable Fluid-resistant mask when there is risk of aerosolization Eye and face protection (except when using Class II, Type A2, B1, or B2 biologic safety cabinet for drug preparation) <p>Certain circumstances also warrant use of respirator appropriate to hazard; National Institute for Occupational Safety and Health–certified (eg, N100 or P100) respirator or self-contained breathing apparatus is appropriate when there is risk of aerosol generation in space without engineering controls (eg, when cleaning out biologic safety cabinet, cleaning up spills, or other emergency situations)</p>
Ventilated cabinets	<p>Class II or III biologic safety cabinet or aseptic containment isolator is required for preparing cytotoxic drugs</p> <p>Biologic safety cabinet must be equipped with continuous monitoring device to allow confirmation of adequate airflow and cabinet performance</p>
Closed systems	<p>Issue of closed systems should be addressed in institutional policies and procedures for handling cytotoxic drugs; closed systems may provide additional layer of protection for staff involved in preparation, administration, or disposal of cytotoxic drugs</p> <p>Closed systems are not acceptable substitute for appropriate ventilation or engineering controls (eg, Class II or III biologic safety cabinets or isolators) used along with personal protective equipment</p> <p>Closed systems may be used for selected cytotoxic drugs; drug packaging may be incompatible with closed system sets in some instances</p>
Syringes and intravenous sets	Needleless vascular access system with Luer lock connections should be used for administration of cytotoxic drugs
Transport and labeling	Cytotoxic drugs must be transported in containers designed to contain leakage and spills and be clearly labeled as containing hazardous drugs
Education and training	<p>All staff who work with or may be exposed to cytotoxic drugs must have appropriate hands-on and educational training during orientation and at least annually thereafter</p> <p>Training should cover potential health risks of cytotoxics, safe practices, containment systems, sources of information, appropriate personal protective equipment, and procedures for handling spills</p> <p>Employer is responsible for orientation and ongoing training and will cover associated costs</p>
Pregnancy	<p>Alternative duties should be offered to individuals who are pregnant or breastfeeding, because possible reproductive risks are associated with exposure to cytotoxic drugs</p> <p>All staff should be fully informed of reproductive hazards</p>
Surveillance	<p>Medical surveillance is not recommended, because adequate tests are not available for monitoring exposure to cytotoxics or assessing level of risk associated with exposure</p> <p>Panel strongly urges additional research to determine if adverse health effects result from exposure of health care workers to cytotoxic drugs and to develop sensitive, specific surveillance tests to detect any adverse health effects</p>
Ethics	Health care facilities have moral and ethical obligations to people who handle cytotoxic drugs to minimize exposure

NOTE. The full set of recommendations can be found at <http://www.cancercare.on.ca/pdf/pebccytos.pdf>.

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