How to improve the safety of chemotherapy administration

Exposure to chemotherapy drugs is more common among health care workers than is generally recognized. A drug transfer system can help.

Preparing chemotherapy treatment under a laminar air-flow hood

BRYANT FURLOW

The cytotoxic drugs used to combat tumor cells can also harm normal cells and their DNA, and these drugs represent a significant occupational exposure risk for hospital pharmacy and infusion center personnel.[1] Occupational exposures can cause acute symptoms such as nausea and skin and eye irritation. Such exposures have also been tied to significantly increased rates of DNA damage, infertility, miscarriage, premature birth, and congenital problems among prenatally-exposed children, including low birth weight, learning disabilities, and limb abnormalities.[1-3] The teratogenic risks are well-established for interferon alfa-2b, leflunomide, methotrexate, thalidomide, and tositumomab, for example.[1] Many anticancer drugs are also known or probable carcinogens and are believed to be at least partly responsible for increased cancer rates among health care workers (**Table 1**).[1,4,5]

Completely safe levels of occupational exposure to these drugs—even in their diluted forms— have not been established, leading US occupational health agencies to champion an "as low as reasonably achievable" (ALARA) approach to the handling and preparation of these drugs by health care personnel.[6,7] Simply put, the goal should be to avoid occupational exposures altogether.[8] In 1986, as a step toward that goal, the US Occupational Safety and Health Administration (OSHA) released guidelines and recommendations intended to prevent occupational exposures among health

care workers. (These guidelines were updated in 1999 and are summarized in **Table 2**.)

CONTAMINATION: UNDERRECOGNIZED AND EXTENSIVE

Exposures may result from direct skin contact or inhalation of vapors, dusts, or aerosols during drug preparation or administration, or from indirect exposure to contaminated surfaces, such as drug vials.[1,7,9] Indirect exposures are a frequently underappreciated route of occupational exposure to these drugs. In 1998, the officials at M.D. Anderson Cancer Center in Houston, Texas, were shocked to discover the extent of environmental contamination with anticancer agents at their facility.

"We had someone come in and do wipe samples where we were preparing IVs," recalled staff pharmacy manager Susan Spivey, PharmD, DDS, R.Ph. "They took samples in the pharmacy, at the hoods, and then in the halls and the nursing units." (Dr Spivey served as an advisor to the Swedish firm Carmel Pharma until 2009, she said. Carmel manufactures PhaSeal, a drug transfer device reviewed in this article.)

Because staff members observed the 1986 OSHA safe-handling guidelines, Dr Spivey and her colleagues had been overconfident, she said in retrospect. "We thought we would come out fine," Dr Spivey said. "We were wrong. We had contamination all over the IV room, outside where pharmacists had been, and up and down the hallway to the nursing unit. It was a surprise. I had thought if we had any contamination, it would be limited to the pharmacy."

Dr Spivey's primary concern was for the potential harm to infusion staff, but given the extent of the contamination, she also worried about visitors to the center. My concern "was global, all the way down to not exposing patients and family members—or anybody else who was around the IV pharmacy," Dr Spivey said. "But the main concern was that the more you encounter it, the greater the chances of contamination or repeated contamination you have, the greater your chances are of harm. Onetime exposures from walking through the area are not going to [involve the same risk]. But these are carcinogens, and some of the risks start with pregnancy—having miscarriages or low-weight babies, or babies with developmental problems and inappropriate limb growth. Exposures can years later lead to acute leukemias."

These chemotherapy agents are carcinogens, and repeated exposures can cause birth defects or lead years later to acute leukemias.

Table 1. Anticancer agents and regimens classified as carcinogens by the International Agency for Research on Cancer[1,4,5]

Known human carcinogens	
• Arsenic trioxide	• Azathioprine
• Chlorambucil	• Chlornaphazine
• Cyclophosphamide	• Etoposide-Cisplatin-Bleomycin (ECB)
• Melphalan	• Mustargen-Oncovin-Procarbazine-Predisone (MOPP)
• Myleran	• Semustine
• Tamoxifen	• Thiotepa
• Treosulfan	
Probable human carcinogens	
• Azacitidine	• Carmustine (BCNU)
• Chlorozotocin	• Cisplatin
• Doxorubicin HCl	• Etoposide
• Lomustine (CCNU)	• Mechlorethamine HCl
• *N*-ethyl-N-nitrosourea	• *N*-Methyl-nitrosourea
• Procarbazine HCl	• Tenioposide

THE EVOLUTION OF GUIDELINES

OSHA's 1986 guidelines were updated in 1999 and remain a core strategy for avoiding environmental contaminations and occupational exposures involving antineoplastic agents. The guidelines recommend periodic testing of ventilation systems and protective equipment, the use of personal protective equipment and hand hygiene practices, and the availability to all staff, contractors, and employees of a written Hazardous Drug Safety and Health Plan describing exposure-prevention practices.[7] The OSHA guidelines recommend that designated hazardous drug handling areas be established, that dedicated biological safety cabinets (BSCs) be used to contain hazardous agents and reduce exposure risk during dose preparation, and that personal protective equipment—including gowns, gloves, respiratory protection, and eye, nose, and mouth protection—be used consistently during dose preparation.

M.D. Anderson was not the only facility with concerns about contamination and exposure despite observance of OSHA guidelines. In 2004, the National Institute for

Occupational Safety and Health (NIOSH) issued an alert calling for additional safe-handling guidelines, including the use of closed-system drug transfer devices (CSTDs), defined as self-contained systems that prevent the escape of hazardous drugs or drug vapors (**Table 2**).[8]

Table 2. Summary of NIOSH recommendations for preventing occupational health care exposures to hazardous drugs

1. Evaluate workplace hazards, the drugs handled, the volume and frequency of their handling, equipment maintenance, decontamination, and waste handling.
2. Handle drugs safely; establish policies and procedures for labeling, storing, and handling drugs; provide training for appropriate handling, spill clean-up, and hygiene practices—hand washing, decontamination, and not allowing eating or drinking in the pharmacy or clinic.
3. Use and maintain equipment properly; use ventilated cabinets, CSTDs, needle-free systems, and personal protection equipment like gloves, gowns, and eye, nose, mouth, and respiratory protection.

PROTOTYPE TO PRACTICE

By 2004, M.D. Anderson was well ahead of most US cancer centers, already using CSTDs, in part because it had helped develop prototypes through collaborations with Carmel Pharma, Dr Spivey said. CSTDs were a newly emerging technology when M.D. Anderson started looking into better isolation controls in 1999, Dr Spivey said, and Carmel's PhaSeal was the only CSTD on the market.

"It was being used in Sweden on a very, very small level," Dr Spivey said. "Oncology nurses were using it on countertops to mix chemo agents there. The prototype came to Houston, and we used it in the first study and found a lot of problems. They took it back to Sweden and made the fixes, and we've used it ever since." Among the problems M.D. Anderson identified in the early PhaSeal system, Dr Spivey told *Oncology Nurse Advisor*, were loose fittings that caused leaks and malfunctioning spikes that didn't always work with IV bags, leading to leaks.

A COSTLY PREVENTIVE

Six years after NIOSH's 2004 recommendation that chemotherapy centers adopt CSTDs, several large US cancer centers contacted by *Oncology Nurse Advisor* had not yet done so. But Dr Spivey, having coauthored several comparative studies, is frequently consulted by hospitals looking into adopting one, and she says people contacting her lately have sounded more "serious" than in the past.

"We don't currently use a closed system but we are in the process of reviewing them so that we can switch over," said University of New Mexico (UNM) Cancer Center oncology pharmacist Stanley Cheshire, PharmD. UNM is currently reviewing the sparse empirical literature of comparative studies to decide which of the available systems will best fit its needs.

"There are very few comparison articles," noted Martin Martinez, PhD, who is heading up UNM's search. Dr Martinez planned to search out and evaluate published and unpublished studies through March 2010, he told *Oncology Nurse Advisor.*

Steep costs remain a big barrier to widespread adoption, particularly in a cost-containment era—and will remain prohibitive for smaller centers into the near future, Dr Spivey believes. Drug transfer devices "cost between $8 and $12 per dose," she said. "PhaSeal is the most expensive one. We find that our cost (with the PhaSeal system) is close to $12 per dose." That comes to an average of $1.5 million a year at M.D. Anderson, noted Dr Spivey, and costs have not declined as additional manufacturers have joined the market with new

Table 3. Drug transfer devices

Device	Manufacturer	Web site
Alaris Smart Site vented vial access device	Cardinal Health	www.alarismed.com/na/products/ecat.shtml
Chemo Mini-Spike Plus dispensing pin	B. Braun Medical, Inc	www.bbraunusa.com/images/bbraun_usa/admix_chemo.pdf
ChemoProtect Spike	Codan US	
PhaSeal Protector 50 and Injector Luer Lock	Carmel Pharma	www.carmelpharma.com/phaseal.html
Tevadaptor vial and syringe adaptor system (marketed in US as OnGuard)	Teva Medical, Israel	www.tevadaptor.com/Products.aspx

products. "Smaller centers probably just aren't going to be able to afford it," she acknowledged.

There are not yet billing codes specific to CSTD equipment, and Medicaid and Medicare do not reimburse for the procedure. It primarily benefits health care workers rather than patients, which doesn't fit neatly into a fee-for-patient-service approach to medical reimbursement. "We try to capture some of the charging in the IV patient bag charge," Dr Spivey explained. "Manufacturers are working hard to get a (billing) code, and everything will explode at that point."

Chemotherapy drug transfer devices should always be utilized in the context of BSCs and vigilant attention to OSHA and NIOSH guidelines.

AN EVOLVING EVIDENCE BASE

Drug transfer devices are a young technology with competing designs and poor market penetration, and the meager published literature on these devices remains dominated by manufacturer-sponsored studies. No meta-analyses or systematic reviews of those studies were located in recent searches of several medical literature archives and databases.

Designs vary from physically closed systems with an expanding balloon to accommodate air pressure differentials (the *PhaSeal* approach), to compartmentalized isolators that employ sealed hoods with fixed gloves, to filter-based systems like the *Tevadaptor* that remove particles and vapors from air passing through the device. (**Table 3** has a list of equipment and manufacturers.)

The largest comparative study to date was published in 2008 by Dr Spivey and colleagues at M.D. Anderson; Clarian Health of Indianapolis, Indiana; and the University of Utah in Salt Lake City (**Table 4**). Although the study itself was not sponsored by Carmel Pharma, Dr Spivey told *Oncology Nurse Advisor*, both she and coauthor James Jorgenson were at that time paid advisors to the company.

The team compared *PhaSeal* with four other drug transfer devices, testing whether or not titanium tetrachloride, a drug vapor simulant, escaped from connections between vial and syringe during preparation or from syringe and port during administration.[8] When titanium tetrachloride contacts water particles in the air, it forms hydrochloric gas and titanium dioxide, which in turn create visible smoke. Photographs were taken of released smoke, indicating the probable escape of drug vapors. Four of the five systems tested leaked, with only Carmel's PhaSeal evincing no escaped smoke.[8]

Dr Spivey and Howard Ritter at M.D. Anderson subsequently tested the dry vial/syringe connections and syringe/access port connections for *PhaSeal*, *Tevadaptor* (*OnGuard*), and *Alaris SmartSite* vented vial access device. They added a fluorescent indicator solution to empty 20-mL vials capped with a rubber stopper and vial cap. Photographing the vials under ultraviolet (UV) light to visualize leaks during syringe withdrawal and reinjection of indicator solution, simulating drug preparation in the pharmacy, and a 7-mL push using the syringe adaptor and IV port for each product to simulate administration to the patient, Dr Spivey and Ritter showed that, again, only PhaSeal's dry connections prevented the escape of the fluorescent solution (**Table 4**).[8]

Leaking filters and membranes caused the observed leaks, Dr Spivey said. While all of the tested devices likely *reduce* liquid or vapor escape during preparation and administration, the authors argue that only PhaSeal meets the strict definition of a truly *closed* (self-contained) drug transfer device that can prevent leaks.[8] "PhaSeal is more expensive than anything on the market, but we consider them the only true closed-system on the market," Dr Spivey suggested.

No drug transfer device is a magic bullet, Spivey was quick to add, and these devices should always be used in the context of BSCs and vigilant attention to OSHA and NIOSH guidelines.

Table 4. Results of pharmacy preparation and patient administration simulation tests [8]

PREPARATION PHASE SIMULATION		
Model	**Vial adaptor/ access leaks**	**Syringe adaptor leaks**
PhaSeal	0 of 15 test runs	0/15
Tevadaptor (*OnGuard*)	10/15	7/15
Alaris SmartSite	13/15	13/15
ADMINISTRATION PHASE SIMULATION		
Model	**Syringe adaptor leaks**	**Port adaptor leaks**
PhaSeal	0 of 15 test runs	0/15
Tevadaptor (*OnGuard*)	9/15	9/15
Alaris SmartSite	13/15	13/15

When testing out new equipment, users should be particularly vigiliant for evidence of leaking filters and membranes at interfaces.

TEST-DRIVE THE TECHNOLOGY

Competition among manufacturers is keen, Dr Spivey noted—and cancer centers can make that work to their advantage. "Don't believe those sales guys," she said. "Test it all out yourself. They should be perfectly willing to give you sample supplies to learn the system and test it out yourself. It's not a bad idea to ask to test the system for a few weeks, so your people have time to see what problems emerge as they use it over time."

Once staff members become familiar with a system, overall preparation times should drop significantly. "If you don't have to worry about vial pressures squirting drugs out, or spills—if you take those out of the link—it makes you more confident," Dr Spivey explained. "Fewer problems occur that can cause contamination."

Most manufacturers will send on-site trainers to show staff how to use the equipment, she said. The biggest challenge for new users of *PhaSeal* is mastering equalization pressures when the drug and air are pushed into a vial, Dr Spivey pointed out. "Sometimes it creates negative pressure and the balloon doesn't work," she explained. "Where to push air to create positive pressure becomes obvious, but you have to learn how to do that by trial and error."

When testing new equipment, be particularly vigilant for evidence of leaking filters and membranes at interfaces, Dr Spivey advised. Testing equipment in the pharmacy doesn't have to involve sophisticated simulations with titanium tetrachloride or fluorescent solutions. Lemon juice will do. "Try putting lemon juice in a vial and testing the product, and then touching it to litmus paper to make sure the outside membranes aren't leaking," Dr Spivey suggested. She warned, "Most will." ■

Bryant Furlow is a medical writer in Albuquerque, New Mexico.

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