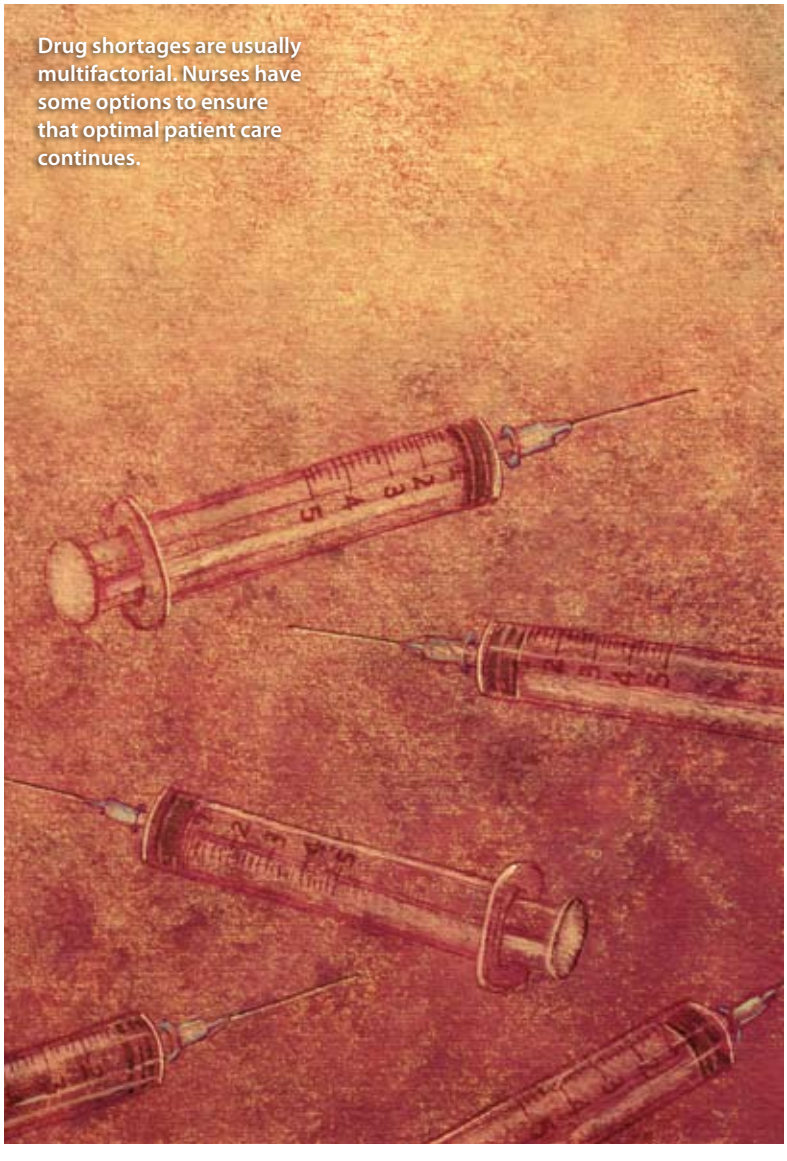
Understanding and managing drug shortages in oncology

Disruptions in supply impact patient care. Nurses should know when to use a substitution drug and when to wait for the next shipment.



Drug shortages are usually multifactorial. Nurses have some options to ensure that optimal patient care continues.

PUNCHSTOCK

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Drug shortages in the United States are becoming increasingly common and, unfortunately, can lead to compromises or delays in treatments or procedures, result in medication errors, and have an unknown clinical impact on affected patients.[1,2] In a recent survey conducted by the Institute for Safe Medication Practices (ISMP), more than 1,800 health care professionals expressed that drug shortages have negatively impacted public health, and even considered it a national health care crisis.[1] The drug-shortage crisis has been unavoidable in most areas of practice, and one of the most significantly impacted specialty areas is oncology. Approximately 20 chemotherapeutic agents, most of which are widely used generics that are a staple in many cancer-treatment regimens, are currently at shortage levels.[3] Drug shortages are frustrating and make caring for our oncology patients difficult at times, and the problem is complex and multifaceted with no easy answers in sight. Nurses should understand what causes a drug shortage and how it impacts health care institutions before addressing the impact on oncology practice.

CAUSES OF A SHORTAGE

The cause of a drug shortage is most often multifactorial, but almost always starts with the pharmaceutical manufacturers. Complicating the matter is that pharmaceutical industries are *recommended* to contact the Food and Drug Administration when a drug shortage or

TABLE 1. Potential medication errors resulting from a drug shortage[1,12,13]

Issue	Example(s)	Medication error
Different regimen may have a different toxicity profile	Change from FOLFOX to CapOx/XelOx during leucovorin drug shortage	Results in increased GI toxicity related to capecitabine over conventional 5-fluorouracil
Discontinuation or shortage of a strength, concentration, or dosage form	• Cytarabine IV Commercially available products listed below: — Powder for reconstitution: » 20 mg/mL 50 mL (1 g) vials » 20 mg/mL 25 mL (500 mg) vials — Solution: » 100 mg/mL 20 mL (2 gram) vials » 20 mg/mL 50 mL (1 gram) vials	Currently there is a drug shortage of all forms of commercially available cytarabine, leading to inconsistent and/or mixed supplies of the powder for reconstitution and solution, which are two different concentrations (20 mg/mL and 100 mg/mL); mix-ups during compounding with incorrect concentration (eg, pharmacist calculates dose using 100 mg/mL concentration, but has 20 mg/mL in stock) results in under- or overdose of drug
	• Etoposide IV	Oral dose is 2x IV dose, which can result in an underdose when oral dosage is used inappropriately
Dose of primary treatment agents varies from dose of alternative treatment agents	• Levoleucovorin interchanged with leucovorin in FOLFOX	Levoleucovorin dose is 50% lower than leucovorin dose when used in FOLFOX; failure to adjust dose properly can result in an overdose of levoleucovorin
	• Vincristine or vinblastine used interchangeably in some chemotherapy regimens	Vinblastine dose is typically 4-20 mg/m^2, whereas vincristine dose is typically 0.7-1 mg/m^2; mix-ups during compounding can result in either under- or overdose of either agent

Key: CapOx/XelOx, capecitabine, oxaliplatin; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin.

Drugs mentioned: 5-fluorouracil (Adrucil, generics); capecitabine (Xeloda); cytarabine (Cytosar-U, DepoCyt, generics); etoposide (Etopophos, generics); leucovorin; levoleucovorin (Fusilev); oxaliplatin (Eloxatin, generics); vinblastine (Velban, generics); vincristine (Oncovin, Vincasar, generics).

limitation in supply is anticipated. Despite the FDA urging to forewarn of a drug shortage, however, pharmaceutical manufacturers are not *required* to provide such warning, and often do not.[4,5] The result is a sudden and unanticipated discontinuation of a medication's supply chain that leaves clinicians with the daunting and cumbersome task of allocating available stock to those patients with the greatest need and finding alternative therapies for the others.[4] Although there is proposed legislation requiring drug manufacturers to provide 6 to 12 months' advanced notice of market withdrawals, issues in supply chain or raw materials, or any foreseeable hurdles to the drug manufacturing process to the FDA and health care providers,[6] the industry does not always have the ability or time to give advance notice of erratic influences on production such as voluntary recalls, lack of raw materials, and natural disasters.

A substantial concern is the industry's lack of adherence to Good Manufacturing Practices (GMPs), which the FDA administers and enforces in the United States. GMPs include manufacturing policies and procedures for developing high-quality medications, dietary supplements, medical devices, diagnostic chemicals, and food products.[7] Most countries have a standard set of GMPs for their pharmaceutical industry; however, the FDA standards are notoriously stricter than GMPs in other countries and are dependably enforced, resulting in higher expectations for compliance in the United States. The intent of the high level of FDA enforcement is to ensure superior quality products are produced and to protect the health and safety of the American public, but this can unintentionally result in an unexpected freeze of the drug supply. When the FDA determines that production of a particular drug does not meet its GMPs, it has the ability to cease further production but not the legal authority to require the manufacturer to comply within a specific time frame or to continue manufacturing the drug in question at all. For generic drugs, compliance with GMPs may cost the manufacturer more money than it would lose by discontinuing production of the drug; therefore, the manufacturer may not pursue manufacturing generic drugs. Such was the case with hyaluronidase, a commonly used antidote for chemotherapy-induced extravasations, leaving no such supplier to date.[8] Depending on the medication in question, the FDA can conduct a medical necessity evaluation and petition another manufacturer to continue or start production of a drug,[5] or allow the drug to be imported from a foreign country until GMP standards are met.[5] In the interim, however, a drug shortage may result.

Athough difficulties with regulatory issues and manufacturing obstacles appear to be a big piece of the drug-shortage

TABLE 2. Possible chemotherapy treatment options during a drug shortage[16]

Chemotherapy drug on shortage	Cancers affected	Options
Asparaginase	Acute leukemias	Change to pegaspargase or omit from regimen
Bleomycin	Hodgkin lymphoma	Omit from regimen
	Testicular cancer	Use an alternative regimen (VIP)
Doxorubicin	Breast cancer	Change to epirubicin
	Hodgkin lymphoma	Use an alternative or salvage regimen (BEACOPP or Stanford V minus doxorubicin, ICE, GDP)
	Non-Hodgkin lymphoma	• Delay treatment if shipment is expected soon • If administering CHOP, change regimen to CNOP
	Osteosarcoma (pediatrics)	Change to daunorubicin
	Sarcomas	Change to epirubicin
Etoposide IV	Lung cancer	Change to oral formulation
Leucovorin	Colorectal carcinoma	Change to levoleucovorin or CapOx/XelOx regimen
Mitomycin	Hepatocellular carcinoma	• Change to chemoembolization regimen not utilizing mitomycin • Delay chemoembolization until mitomycin available
Vincristine	Acute leukemias	Omit from regimen
	Non-Hodgkin lymphoma	Omit from regimen
	Wilms tumor	Change to vinblastine, if available
Vinblastine	Hodgkin lymphoma	• Change to a salvage regimen (see doxorubicin) • Omit from regimen
	Melanoma	Change to vincristine, if available
	Wilms tumor	Change to vincristine, if available

Key: BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CapOx/XelOx, capecitabine, oxaliplatin; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CNOP, cyclophosphamide, mitoxantrone, vincristine, prednisone; GDP, gemcitabine, dexamethasone, cisplatin; ICE, ifosfamide, carboplatin, etoposide; Stanford V, doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone; VIP = vinblastine, ifosfamide, cisplatin

Drugs mentioned: 5-fluorouracil (Adrucil, generics); asparaginase (Elspar); bleomycin (Blenoxane, generics); capecitabine (Xeloda); carboplatin (Paraplatin, generics); cisplatin (Platinol, generics); cyclophosphamide (Cytoxan, Neosar, generics); cytarabine (Cytosar-U, DepoCyt, generics); dacarbazine (DTIC-Dome, generics); daunorubicin (Cerubidine, DaunoXome, generics); dexamethasone (Decadron, Dexamethasone Intensol, Dexpak Taperpak, generics); doxorubicin (Adriamycin, Doxil, Rubex, generics); epirubicin (Ellence, generics); etoposide (Etopophos, generics); gemcitabine (Gemzar, generics); ifosfamide (Ifex, generics); leucovorin; levoleucovorin (Fusilev); mechlorethamine (Mustargen); mitomycin (Mutamycin, generics); mitoxantrone (Novantrone, generics); oxaliplatin (Eloxatin, generics); pegaspargase (Oncaspar); prednisone; procarbazine (Matulane); vinblastine (Velban, generics); vincristine (Oncovin, Vincasar, generics).

issue, there are other contributing factors. Disruptions in the flow or supply of raw materials used in the pharmaceutical manufacturing process may further exacerbate or cause a drug shortage. Up to an estimated 80% of raw materials used in pharmaceutical manufacturing are obtained from outside the United States.[7] Political instability, climatic change or natural disaster, or issues with contamination of either plants or animals can abruptly and uncontrollably interfere with the importation of raw and bulk materials. This is especially problematic when the sole supplier is from one particular region. Other examples can be voluntary recalls, often relating to minor manufacturing issues outside of FDA regulatory control; changes in product formulation (eg, the chemical propellants in albuterol metered-dose inhalers were changed in 2006); or simply the business decision of the manufacturer to halt production due to low revenue or decreased demand.[2] In addition, mergers and acquisitions among pharmaceutical companies are becoming increasingly common, and their efforts to streamline the manufacturing process may also cause delays or shortages in a drug's availability.

IMPACTS ON THE HEALTH CARE SYSTEM

The immediate effects of a drug shortage are easily comprehensible: patients may or may not get a medication that they require to treat their medical illness or may be treated with an alternative or second-line agent. Further consideration reveals additional problems involving stockpiling and distribution. Unlike other issues between the FDA and

pharmaceutical manufacturers, these concerns are directly tied to health care institutions and their actions in response to a drug shortage. Although the intent is to provide the utmost quality of care to patients, their actions may inadvertently worsen or prolong a drug shortage.[5]

One such action is stockpiling drugs. *Stockpiling* is defined as buying a larger-than-needed supply of medications either in response to or in anticipation of a drug shortage. This can directly create or prolong a drug shortage by reducing the amount of drug available to other health care institutions.[8,9] Another common practice is to stockpile the second-line or alternative agent in anticipation of need secondary to a drug shortage (eg, stockpiling epirubicin [Ellence, generics] during the doxorubicin [Adriamycin, Doxil, Rubex, generics] shortage in 2010). This is risky for an institution; if the drug shortage is anticipated and never occurs, the institution is financially responsible for a bulk supply of a drug that may never get used.[9] Most manufacturers typically respond to a drug shortage by allocating a supply of the drug based on previous sales. The bulk purchase of a drug in anticipation of a shortage rarely, if ever, effects this allocation. Furthermore, a given drug may have a lengthly lead time, meaning the time from raw materials to patient use is comparatively prolonged. The manufacturer may have ample time to correct the issue before the shortage ever affects the end-user. Therefore, most professional organizations, including the American Society of Health-System Pharmacists (ASHP) and the National Comprehensive Cancer Network (NCCN), strongly advise against health care institutions stockpiling or hoarding any medications in anticipation of or in the event of a drug shortage.[10,11]

Drug shortages can also lead to the use of nontraditional wholesalers and suppliers, frequently termed as the *grey market*.[2,4] Typically, grey market wholesalers obtain a small supply of a medication either immediately before or after a drug shortage is announced, then offer the drug to health care institutions, physician practices, nursing homes, et cetera, at an inflated price. As the origin of grey market drugs is either unknown or derived from foreign markets, there is no guarantee of the drug's pedigree or assurance that the drug was stored and transported appropriately through chains of custody. Similarly, compounding pharmacies have attempted to make drugs on short supply; however, compounded medications are not always subject to the same federal regulations as commercially prepared drugs. Significant concerns exist about the quality of the raw materials used in compounded drugs and the overall product dispensed by these pharmacies.

MANAGEMENT OF DRUG SHORTAGES IN ONCOLOGY PRACTICE

Identifying the major causes of drug shortages and exploring the impact on the overall health care system reveal the complexity of the issue. The impact on oncology may be something as simple as delaying a patient's chemotherapy for several days until a new shipment of drug is allocated, to something more significant such as omitting a drug from a chemotherapy regimen or using a second-line drug in a chemotherapy regimen without a clear picture of the bearing on a patient's cancer treatment—or worse, full knowledge that the alternative therapy is suboptimal to the standard-of-care regimen.

Although no evidence-based or guideline-driven method is in general practice for handling drug shortages, the potential sources for error and some methods for managing these shortages are described. However, the particular ways of handling a shortage are entirely dependent on the type of practice setting and the preference of the treating physician(s).

One related issue arising in oncology practice is an increase in medication errors or near-miss medication errors related to nontraditional changes or alterations to standard-of-care

TABLE 3. Supportive care medications currently on short supply/shortage[16]

Medication	Common use(s)
Amikacin injection (Amikin, generics)	Aminoglycoside antibiotic used in treatment for serious gram-negative infections
Calcium gluconate injection	Electrolyte replacement or cardiac membrane stabilization in hyperkalemia
Dexamethasone (Decadron, Dexamethasone Intensol, Dexpak Taperpak, generics)	Prevention and/or treatment of chemotherapy-associated nausea and vomiting
Foscarnet sodium injection (Foscavir)	Antiviral treatment used for cytomegalovirus (CMV) disease
Furosemide sodium injection (Lasix, generics)	Diuretic used to manage fluid overload
Norepinephrine bitartrate injection (Levophed, generics)	Vasopressor used in treatment for septic shock
Osetalmavir (Tamiflu) oral suspension	Antiviral used in treatment of influenza
Sulfamethoxazole/Trimethoprim (SMX/TMP) injection	Antifolate antibiotic used in treatment for a variety of bacterial infections

regimens. The National Coordinating Council for Medication Error and Prevention (NCC MERP) defines a *medication error* as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer."[12] A *near miss,* on the other hand, is defined by the Institute of Safe Medication Practices (ISMP) as a medication error that is captured and corrected by active efforts on the part of the health care team prior to reaching the patient.[13] A recently published ISMP survey regarding drug shortages reported that 35% of respondents had been involved in or witnessed a near-miss medication error, 25% responded that an error actually occurred, and 20% claimed the error had a negative impact on the patient.[1] Recognizing that a particular drug strength, concentration, or dosage form may be on short supply is important, and health care professionals need to be on the lookout for such confusion. **Table 1** outlines some potential causes of medication errors during a drug shortage. All health care professionals who treat oncology patients—from physicians to pharmacists, to nurses—are responsible for ensuring that these types of errors do not occur.

The multidisciplinary oncology team is charged with providing patient-focused and quality care despite our current drug supply issues.

Although some chemotherapy protocols have available alternatives, clinicians are still faced with the dilemma that not all options have been assessed or researched clinically, and not all chemotherapy regimens or disease states have a viable alternative. **Table 2** presents some options or alternatives that resulted from recent chemotherapy drug shortages. The impact on overall survival in patients who were switched from asparaginase (Elspar) to pegaspargase (Oncaspar), 5-fluorouracil (Adrucil, generics) to capecitabine (Xeloda), and leucovorin to levoleucovorin (Fusilev) is unknown. In fact, FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin [Eloxatin, generics]) has been compared with only CapOx/XelOx (capecitabine, oxaliplatin) in randomized clinical trials of colorectal cancer in the metastatic setting;[14] however, because of the leucovorin shortage, clinicians were making this switch in the adjuvant setting where no data exist. In addition, significantly more GI toxicity was noted with CapOx/XelOx than with FOLFOX.[1] In this example, not only is the overall impact on survival unknown, but additional impacts on patients' quality of life occurred.

In some cases, head-to-head comparisons of regimens may exist, but concerns about the efficacy or toxicity reported in the results may exist. For example, a direct, randomized comparison of ABVD (doxorubicin [Adriamycin, Doxil, Rubex, generics], bleomycin [Blenoxane, generics], vinblastine [Velban, generics], dacarbazine [DTIC-Dome, generics]) and MOPP (mechlorethamine [Mustargen], vincristine [Oncovin, Vincasar, generics], procarbazine [Matulane], prednisone [Prednisone Intensol, Sterapred, generics]) for Hodgkin lymphoma treatment demonstrated that both regimens were equal in terms of efficacy, but differed in regards to toxicity.[15] Patients receiving MOPP experienced significantly more nausea/vomiting, secondary cancers, and sterility compared with patients receiving ABVD. The last two side effects are important considerations in a highly curable disease for which the median age of diagnosis is approximately 25 years, and patients are expected to live 40+ years posttreatment. In other instances, the second-best alternative agent, levoleucovorin (used during the leucovorin shortage), can become scarce as well, usually because of the increased demand. This may force clinicians to resort to using third- and fourth-line regimens to treat patients. Front-line chemotherapy agents are not the only drugs affected either; commonly used supportive medications can be an issue as well (**Table 3**). Supportive care medications, however, typically have more alternatives and the outcomes are more easily assessed.

CONCLUSION

Overall, drug shortages are frustrating, intricate, and multilayered. The complexity of the manufacturing process, the FDA and its authoritative role, inappropriate use of grey markets, and the economic burden of drug shortages compound the issue further and make the solution to the drug-shortage dilemma seem impossible to attain. Despite the availability of alternatives in most circumstances, the impact on outcomes for oncology patients, for the most part, cannot be characterized and is unknown at this time. However, the multidisciplinary oncology team is charged with the responsibility for continuing to provide the utmost in patient-focused and quality care despite the circumstances surrounding our current drug-supply issues. ■

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REFERENCES

1. Institute for Safe Medication Practices (ISMP). Special issue: drug shortages national survey reveals high level of frustration, low levels of safety.

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ISMP Medication Safety Alert! Acute Care. Published September 24, 2010. http://www.ismp.org/Newsletters/acutecare/articles/20100923.asp. Accessed May 13, 2011.

2. ASHP Expert Panel on Drug Shortages, Fox ER, Birt A, James KB, et al. ASHP guidelines on managing drug product shortages in hospitals and health systems. *Am J Health Syst Pharm*. 2009;66(15):1399-1406.
3. Slama L. Oncology drug shortage rising. Health Leaders Media Web site. Published February 18, 2011. http://www.healthleadersmedia.com/page-1/HOM-262817/Oncology-Drug-Shortage-Rising. Accessed May 13, 2011.
4. Tyler LS, Mark SM. Understanding and managing challenges posed by drug shortages. Proceedings of a breakfast symposium held during the 37th annual ASHP Midyear Clinical Meeting; December 9, 2002. http://www.ashp.org/s_ashp/docs/files/DShort_abbott_drug.pdf. Accessed May 13, 2011.
5. Tyler LS, Fox ER, Caravati EM. The challenge of drug shortages for emergency medicine. *Ann Emerg Med*. 2002;40(6):598-602.
6. Summary of a stakeholders' meeting on drug shortages convened by the American Medical Association and the American Society of Health-System Pharmacists. Provisional observations of drug product shortages: effects, causes, and potential solutions. *Am J Health Syst Pharm*. 2002;59(22):2173-2182.
7. Fox ER, Tyler LS. Managing drug shortages: seven years' experience at one health system. *Am J Health Syst Pharm*. 2003;60(3):245-253.
8. American Society of Anesthesiologists, American Society of Health System Pharmacy, American Society of Clinical Oncology, Institute for Safe Medication Practices. Drug Shortages Summit Summary Report. November 5, 2010; Bethesda, MD. http://www.ashp.org/drugshortages/summitreport. Accessed May 13, 2011.
9. Li EC. Coping with drug shortages. National Comprehensive Cancer Network Web site. http://www.nccn.org/about/news/ebulletin/2011-02-07/drug_shortages.asp. Accessed May 13, 2011.
10. Thompson CA. Drug shortage broaches ethics of buying in excess. *Am J Health Syst Pharm*. 2009;66:610-611. doi:10.2146/news090032.
11. Frequently Asked Questions. Institute for Safe Medication Practices Web site. http://www.ismp.org/faq.asp. Accessed May 13, 2011.
12. What is a medication error? National Coordinating Council for Medication Error Reporting and Prevention Web site. http://www.nccmerp.org/aboutMedErrors.html. Accessed May 12, 2011.
13. ISMP survey helps define near miss and close call. ISMP Medication Safety Alert! Acute Care. http://www.ismp.org/Newsletters/acutecare/articles/20090924.asp. Accessed May 13, 2011.
14. Cassidy J, Clark S, Diaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol*. 2008;26(12):2006-2012.
15. Canellos GP. Can MOPP be replaced in the treatment of advanced Hodgkin's disease? *Semin Oncol*. 1990;17(1 suppl 2):2-6.
16. Current drug shortages. US Food and Drug Administration Web site. http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050792.htm. Accessed May 13, 2011.