Ethical Challenges: Managing Oncology Drug Shortages

John Valgus, PharmD, Eric A. Singer, MD, MA, Scott R. Berry, MD, MHSc, and W. Kimryn Rathmell, MD, PhD

North Carolina Cancer Hospital; University of North Carolina Lineberger Cancer Center, Chapel Hill, NC; The Cancer Institute of New Jersey; University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, New Brunswick, NJ; Sunnybrook Odette Cancer Centre; and University of Toronto, Toronto, ON, Canada

Abstract

This vignette highlights the ethical issues surrounding restricted access to oncology drugs caused by drug shortages. A review of selected literature and a framework for creating institutional guidelines for reacting to shortage is provided.

M.A. is a 12-year-old male who is undergoing treatment for acute lymphoblastic leukemia. He is currently in the induction phase of his chemotherapy and is scheduled to receive CNS prophylaxis with weekly intrathecal (IT) methotrexate (MTX). In the same institution, B.M. is a 67-year-old male who is currently being treated for primary CNS lymphoma with high-dose MTX-based chemotherapy. His symptoms and disease have responded well to therapy, and he is scheduled for admission for his third cycle of chemotherapy. Little do these two patients know, but their respective treatment plans are on a collision course. Over the course of the past month, the institution has slowly depleted its supply of preservative-free MTX to now-critical levels. This is due to a national shortage of preservative-free MTX, with no release date in the near future, based on information provided by the manufacturers of this product.

Luckily for these two patients, the institution has developed a task force to monitor and respond to shortages of critical medications. The group consists of pharmacy, nursing, ethics committee, social work, physician, and patient representatives who work together to develop ways of managing the drug shortages that the institution faces. A number of strategies have been put in place to handle this situation and to ensure that essential life-saving medications are optimally utilized to avoid waste and ensure patients are able to continue with therapy.

Although professional organizations such as ASCO are actively working with the US government to raise awareness of chemotherapy drug shortages and to advance legislative and policy solutions, the current mindset of practicing oncology clinicians has moved from *if* a shortage will affect their practice, to *when* a shortage will change their practice. Not only are clinicians weighing the evidence from clinical trials and tailoring this to their individual patients, but they are also now taking into consideration what pieces of their usual armamentarium are actually available to them. At the front lines, institutions can put in place policies and procedures that help maximize the use of an existing medication supply and if needed, prioritize which patients will receive medications that are at critically low levels. We will use the cases of M.A. and B.M. to highlight some of the steps that can be taken to better prepare a practice or institution for the inevitable drug shortages that we face.

Improving Awareness of Impending Shortages

Much of the work of the federal government has been targeted at providing as much notice as possible to clinicians of impending shortages and at preventing shortages from occurring. Drug manufacturers have been mandated by the Food and Drug Administration Safety and Innovation Act[1] to notify the US Food and Drug Administration of impending shortages at least 6 months in advance or as soon as possible. This in turn will allow institutions and practices to best prepare for a possible shortage. The responsibility still lies, however, on the individual institution to routinely track shortages. This requires the deployment of resources dedicated to this important task in order to identify shortages as far in advance as possible. In the case of the vignette institution, a drug shortage task force had been developed to manage the ongoing drug shortage crisis. This task force tracks professional organization Web sites, such as the American Society of Health-System Pharmacists (www.ashp.org/shortages), which is updated daily, regarding medication shortages.

These resources can provide timely updates on medications currently in shortage, reason for the shortage, existing manufacturers, and expected release dates of future supplies of the given medication. Once a shortage has been identified, several steps can be taken to prepare to manage the shortage. These steps include validating details of a shortage, determining the stock on hand, determining the supply from established and alternative sources, estimating the time to affect the institution or practice, and determining the supply of alternative drug products.[2] Armed with this information, an interdisciplinary team including oncologists, pharmacists, nurses, social workers, ethics committee members, and patient representatives can convene to establish what actions must be taken to address immediate concerns as well as longer term issues. It is essential that ethical priority setting take place before a resource shortage[3] and that strategies be considered to optimize the utilization of the normal supply, utilizing alternative agents when clinically appropriate, and reducing wasted drug when possible.

Developing Strategies to Extend the Existing Drug Supply

One strategy to extend the existing drug supply is through the identification of alternative agents. In many cases, alternative chemotherapy regimens that have a similar efficacy and use nonshortage agents are available. In other scenarios, such as the cases of M.A. and B.M., alternative chemotherapy regimens may be considered inferior to the existing regimen. In these examples, the elimination of IT MTX for a patient with acute lymphocytic leukemia, or of high-dose MTX in the case of primary CNS lymphoma, would result in compromised response rates, or even worse, decreased survival rates. In the case of MTX, alternative formulations of the same medication exist, including injectable MTX preserved in benzyl alcohol.[4] As a result of the preservative, this formulation cannot be used for IT delivery because of the risk of myeloencephalopathy and potential paralysis.[5,6] Infants lack the ability to metabolize benzyl alcohol, which can induce a lethal toxicity. However, MTX preserved in benzyl alcohol at doses of up to 750 mg may be safely used in adult patients.[7] In this case, all intravenous doses less than 750 mg could utilize the preservative-containing product, whereas preservative-free product can be reserved for IT administration and intravenous doses greater than 750 mg.

Another strategy for managing drug shortages is to avoid waste. In the vignette example, the current supply of preservative-free MTX is only available in 250-mg vial sizes. However, the average dose of IT MTX is only 12 mg. Because of the lack of preservative, the shelf life of an opened vial of preservative-free MTX is limited. One can see how a center could generate a large amount of chemotherapy waste when treating a small number of patients, or even a single patient, in a day. A strategy to extend available resources is to cluster all patients who are receiving IT preservative-free MTX to specific days of the week, so that this waste may be minimized while treating as many patients as possible. Oncologists will need to work closely with pharmacy staff to make decisions about how changes in administration days can best be implemented while also being vigilant for any unintended effects on the cancer care plan. In this scenario, the data are supportive of such an approach, as most clinical trials have allowed a range of days where weekly IT doses could be administered. It is also essential that such treatment changes be communicated to patients and their caregivers along with the rationale for making the modifications. This discussion will educate patients about oncology drug shortages, alert them to any changes they need to be mindful of, and prevent them from suffering undue anxiety or misinterpreting the adjusted schedule as a delay in treatment.

Prioritizing Existing Supplies

Unfortunately, even if practices use all of the above strategies, they may still find themselves in a situation where they do not have enough supply to meet their current demands. In this scenario, difficult situations will need to be addressed, including how to best utilize the existing supply for the current population of patients who need it. But how should organizations actually go about making these tough decisions?

Table 1. Key Points: Putting Ethical Priority Setting Into Practice

Relevance
• Develop a rationale for each priority-setting decision.
• Use decision criteria based on your mission, vision and values.
• Collect data/information related to each criterion.
• Consult with internal and external stakeholders to ensure relevance of decision criteria and to collect relevant information.
• Make decisions using a multidisciplinary group of informed stakeholders.
Transparency
• Communicate the decision and its rationale.
• Use an effective communication strategy to engage internal and external stakeholders around priority setting goals, criteria, processes, and decisions.
Revision
• Incorporate opportunities for iterative decision review.
• Develop a formal decision-review process based on explicit decision-review criteria.
Enforcement
• Lead by example (ie, ethical leadership).
• Evaluate and improve the priority-setting process.

A useful ethical framework that has been recommended to help guide these difficult decisions in the context of drug shortages[8] is the accountability for reasonableness (A4R) framework, originally proposed by Daniels and Sabin.[9] Ethicists have been unable to agree on a universally acceptable framework based on principles of distributive justice to guide priority setting decisions. A4R elucidates key principles (Table 1) necessary to establish a fair deliberative process that those facing limits imposed by a rationing strategy would regard as legitimate. Based on the application of this framework to real priority-setting problems, experts in the field have offered guidance on actually putting this framework into practice (Table 1).[3,10]

A key element of the A4R framework is the relevance principle, which states that decisions setting prioritization "should be made on the basis of reasons (ie, evidence, principles, values, arguments) that fair-minded people can agree are relevant under the circumstances."[3] Patients eligible for prioritization might include those who are receiving therapy with curative intent for which no suitable alternative regimen exists, pediatric patients (for whom treatment has a reasonable chance of benefit or cure), those on clinical trials, and those for whom a given drug has been shown to improve overall survival. A strength of the A4R framework is that it can be adapted by individual organizations to set criteria for prioritization based on local factors, values, and deliberations. Table 2 includes a set of criteria that are supported by the A4R framework, or have been successfully utilized by these authors, that could be used by organizations in establishing their own prioritization strategies.

Conclusions

Shortages of essential chemotherapy and supportive medicines are becoming a routine part of oncology practice. Thus, it is now crucial that the management of shortages be adopted as

Table 2. Factors to Consider When Faced With an Oncology Drug Shortage

Indication	Approved indication versus off-label use: Patients being treated with a medication that has an approved indication for their condition should receive priority over off-label uses of a shortage drug. First line versus subsequent line: Patients receiving first-line therapy should receive priority over patients getting second- and subsequent-line therapy.
Goals of care	Curative intent versus palliation: Patients who may be cured of their disease should receive a shortage drug over those whose disease is not curable or who are using the drug for palliation. Best supportive care should be offered to all patients regardless of goals of care, treatment indication, or line of therapy.
Cycle of treatment	Ongoing regimen versus treatment plan being developed: Patients who have started a treatment regimen should receive a shortage drug over those who have not yet started therapy in order to avoid a situation where a patient receives the toxicity of therapy, and possibly that of another agent, but is not able to receive the potential benefit of a full course of the originally intended treatment.
Suitable alternatives	Alternative approved and available versus not: Patients who may be treated with multiple regimens supported by high levels of medical evidence should be encouraged to choose the medication or combination of medications that avoids or uses the least amount of the shortage drug.
Ability to pay	Medical necessity should trump the patient's insurance status and/or financial resources when making allocation decisions. Drug hoarding, gray or black-market purchases, price gouging, and bidding wars are unethical. Market forces certainly do affect health care and oncology, but they should not determine how health care providers handle oncology drug shortages.
Informed consent	Coping with a cancer diagnosis and treatment is extremely difficult when all recommended options are available. The stress, anxiety, and frustration our patients feel because of oncology drug shortages must be considered. In order for patients to make an informed treatment decision, oncologists must communicate • What treatment is recommended • How a shortage will be managed • Likely ramifications of a treatment disruption • Whether alternative treatments, such as surgery, radiation, or another drug/regimen are available
Policy timing	Proactive versus reactive: Oncology drug shortages are a reality and will continue to challenge practitioners and patients alike. Congress and specialty societies are aware of the issue and are working to lessen the likelihood of future events. However, each health system, medical center, and practice must proactively develop plans for how to deal with oncology drug shortages. These plans, like those in place to manage a mass casualty incident, natural disaster, or a pandemic flu outbreak, should be informed by the best science available, be created with the input of diverse stakeholders (physicians, nurses, pharmacists, social workers, patient representatives, ethics committees, etc), and be regularly reviewed and updated.

standard of care guidelines to ensure that patients across the health care system receive appropriate therapy for their disease. This will require a concerted effort within each institution to develop fair, legitimate, and effective strategies for anticipating and managing shortages, as well as communicating the rationale and decisions to physicians, staff, patients, and caregivers.

Authors' Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

Author Contributions

Conception and design: All authors

Collection and assembly of data: All authors

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Correspondence to: W. Kimryn Rathmell, MD, PhD, 450 West Dr, CB 7295, Chapel Hill, NC 27599; e-mail: Rathmell@med.unc.edu.

DOI: 10.1200/JOP.2012.000779; published online ahead of print at jop.ascopubs.org on February 5, 2013.

References

1. US Senate, Committee on Health Education Labor and Pensions: Building a 21st century FDA: Proposals to improve drug safety and innovation (S Hrg. 2007). Washington, DC, US Government Printing Office, 2007

2. ASHP Panel on Drug Product Shortages, Fox ER, A Birt, et al: ASHP guidelines on managing drug product shortages in hospitals and health systems. Am J Health Syst Pharm 66:1399-1406, 2009

3. Gibson JL, Martin DK, Singer PA: Evidence, economics and ethics: Resource allocation in health services organizations. Healthc Q 8:50-5 9, 4, 2005

4. Javadzadeh Y, Hamishehkar H: Enhancing percutaneous delivery of methotrexate using different types of surfactants. Colloids Surf B Biointerfaces 82:422-426, 2011

5. Hahn AF, Feasby TE, Gilbert JJ: Paraparesis following intrathecal chemotherapy. Neurology 33:1032-1038, 1983

6. Saiki JH, Thompson S, Smith F, et al: Paraplegia following intrathecal chemotherapy. Cancer 29:370-374, 1972

7. Kimura ET, Darby TD, Krause RA, et al: Parenteral toxicity studies with benzyl alcohol. Toxicol Appl Pharmacol 18:60-68, 1971

8. Rosoff PM: Unpredictable drug shortages: An ethical framework for short-term rationing in hospitals. Am J Bioeth12:1-9, 2012

9. Daniels N: Accountability for reasonableness. BMJ 321:1300-1301, 2000

10. Rosoff PM, Patel KR, Scates A, et al: Coping with critical drug shortages: An ethical approach for allocating scarce resources in hospitals. Arch Intern Med 172:1499-1500, 2012