ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Scarcity of Vital Oncology Drugs: Finding Long-Term Solutions

Richard L. Schilsky, MD
Immediate Past Chair
Government Relations Committee, ASCO
Professor of Medicine
Chief, Section of Hematology-Oncology
The University of Chicago Medicine
Chicago, Illinois

H&O What has the last decade looked like in terms of shortages of oncology drugs?

RLS While there have been periodic shortages of generic injectable oncology drugs throughout the last decade, the number of drugs in short supply has dramatically increased in the last 2 years. When considering all injectable drugs in short supply across all therapeutic areas, the number of drug shortages has tripled since 2006.

H&O What types of agents are in scarce supply?

RLS Essentially, most of the agents in short supply are generic injectable drugs. Among the chemotherapy drugs, those most commonly in short supply have been 5-fluorouracil, racemic leucovorin, etoposide, daunorubicin, doxorubicin, carboplatin, cisplatin, cytarabine, and preservative-free methotrexate. It should be noted that other generic injectable drugs commonly used by cancer patients, including pain medicine and anesthetics, have also frequently been in short supply. The only brand name oncology drug to have been in short supply is Doxil (Janssen Products, LP), a liposomal formulation of doxorubicin.

H&O What is causing these shortages?

RLS The causes of the drug shortages are multi-factorial. It is important to note that 80% of all generic injectable drugs are made by only 5 manufacturers, each of which makes hundreds of generic drug products. The US Food and Drug Administration (FDA) has estimated that 42% of the drug shortages have been related to product quality issues, 18% to reduced production capacity, 18% to voluntary discontinuation of the product line by a manufacturer, and 9% due to raw material shortages and a variety of other causes. Whenever a plant goes offline for quality problems, it must be inspected and re-certified by the FDA before drug manufacturing can resume. Generic drug manufacturers operate on a very narrow profit margin and, in some cases, it may make the most business sense to simply shift production to a different product line rather than invest in the improvements required to resume chemotherapy drug production. New manufacturers cannot easily pick up the slack either, as they must submit an Abbreviated New Drug Application (ANDA) for review and approval to the FDA before beginning to manufacture the drug. Due to staffing constraints, the FDA has close to a 2-year backlog in reviewing such applications. Table 1 outlines some cited reasons for chemotherapy drug shortages.

H&O How have patients, oncologists, researchers, and institutions been affected by the shortages?

RLS For patients, the drug shortages have caused great anxiety about whether they will be able to receive their chemotherapy on schedule, at the appropriate dose, or with the optimal agents. In some cases, patients' lives are at stake when potentially life-saving drugs are not available and there are no acceptable substitutes. Examples of this critical predicament include cytarabine and preservative-free methotrexate for the treatment of adult and childhood leukemia, respectively. For some patients, their

Table 1. Cited Reasons for Chemotherapy Drug Shortages

Increased national and worldwide demand for oncology drugs
Shortages of supply of raw materials
Production problems; contamination of materials
Aging production plants
Limited inventories of generic drugs to reduce company costs
Limited profit margins for generic drugs; Medicare ASP + 6% reimbursement system
Gray market, stockpiling, and price gouging
Private oncologists favoring use of brand name over generic drugs
FDA over-regulation and long timelines to approve new sources of generic drugs

ASP=average sales price; FDA=Food and Drug Administration.
Data from Link MP, Hagerty K, Kantarjian HM. Chemotherapy drug shortages in the United States: genesis and potential solutions. *J Clin Oncol*. 2012;30:692-694.

cost of treatment has increased substantially when a brand name product is substituted for a generic drug, as has often been the case when capecitabine (Xeloda, Roche) has been substituted for 5-fluorouracil and leucovorin. For physicians and pharmacists, the drug shortages have resulted in increased workload and decreased practice efficiency, as a great deal of time has been spent locating alternative supplies of needed drugs, developing priority lists of which patients can be treated when, and identifying potential drug substitutes and modifying treatment plans accordingly. Concerns have also been raised that inadequate supplies of certain drugs can affect accrual to clinical trials or the reliability of research results. When protocol-specified drugs are not available, drug treatment delays or drug substitutions may constitute a technical protocol violation and dampen enthusiasm for enrollment of patients on studies. In the 15-month period from December 2010 to March 2012, the Cancer and Leukemia Group B (CALGB) headquarters office issued 8 notifications of drug shortages that involved 7 different drugs and 23 different protocols for treatment of 7 different tumor types. The notices advised CALGB members to delay patient registration on study, omit certain drugs from the treatment program, substitute certain agents for others in short supply, or, if possible, borrow drugs from neighboring institutions.

H&O What is the ASCO Government Relations Committee?

RLS The American Society of Clinical Oncology (ASCO) Government Relations Committee is a standing committee of ASCO that has responsibility to advise ASCO leadership on policy matters relating to oncology practice or cancer research, as well as to engage with government agencies and Congress on issues important to cancer patients and oncologists.

H&O How has ASCO addressed the problems associated with oncology drug shortages?

RLS ASCO has attempted to address the drug shortage problem in many ways. Largely through the leadership of immediate past-president Michael Link, MD, ASCO worked hard to shine a light on this problem through Congressional testimony and staff briefings, discussions with FDA staff, meetings with the Secretary of Health and Human Services, as well as extensive media outreach to the popular press, the trade press, and through publications in medical and scientific journals.

H&O What actions has the FDA taken?

RLS There are a variety of actions that the FDA can take and has taken to attempt to mitigate the drug shortages, particularly following the issuance of an executive order by President Obama in 2011 requiring them to do so. Although the FDA cannot require any manufacturer to produce a drug, they can request that companies do so, and can provide expedited review of their applications to begin production. The FDA can help identify alternative sources of raw materials that are in short supply, and can also exercise regulatory discretion on drug importation. Through these measures, the FDA estimates that 195 drug shortages (across all therapeutic areas) were prevented in 2011.

H&O What solutions have been proposed, and what is needed in order for there to be a lasting resolution to the drug shortage crisis?

RLS Recently passed legislation that re-authorizes the Prescription Drug User Fee Act (PDUFA) contained many provisions designed to mitigate drug shortages. Manufacturers are now required to notify the FDA 6 months in advance of an impending shortage of a "life sustaining drug," although the law fails to impose penalties for companies that fail to do so. The legislation authorizes the FDA to expedite inspections and reviews based on notifications from manufacturers and permits limited "repackaging" of drugs in short supply within a single hospital or health system. The legislation also gives the FDA expanded authority to inspect foreign manufacturing plants and requires that they keep records of drug shortages, including the number and

causes of shortages, and the steps that have been taken to resolve the shortage. The FDA is required to prepare a trend analysis, and to report annually to Congress and the public regarding the drugs in short supply. This legislation was passed by the US Senate in early May 2012 and was also passed by the US House of Representatives a few weeks later. It was signed into law by President Obama on July 9, 2012.

H&O What does the future hold?

RLS In the last few months, the shortages of generic injectable chemotherapy drugs seem to have abated considerably. It is likely that periodic shortages will persist, and that permanent solutions will require enhancing the business model of generic drug manufacturing, such that these drug makers are able to make a sufficient profit to continue supplying these essential drugs to the American public.

Suggested Readings

US Food and Drug Administration. Prescription Drug User Fee Act (PDUFA). http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm. Accessed August 21, 2012.

US Food and Drug Administration. Prescription Drug User Fee Act (PDUFA) reauthorization. http://www.accessdata.fda.gov/FDATrack/track-proj?program=cder&id=CDER-OPI-PDUFA-Reauthorization. Accessed August 21, 2012.

Kronquist AR. The Prescription Drug User Fee Act: history and reauthorization issues for 2012. Washington, DC: The Heritage Foundation, December 21, 2011. http://www.heritage.org/research/reports/2011/12/the-prescription-drug-user-fee-act-history-and-reauthorization-issues-for-2012. Accessed August 21, 2012.

Link MP, Hagerty K, Kantarjian HM. Chemotherapy drug shortages in the United States: genesis and potential solutions. *J Clin Oncol*. 2012;30:692-694.

Gatesman ML, Smith TJ. The shortage of essential chemotherapy drugs in the United States. *N Engl J Med*. 2011;365:1653-1655.

Hunnisett-Dritz D. Successful importation of cytarabine into the United States during a critical national drug shortage. *Am J Health Syst Pharm*. 2012;69:1416-1421.

Havrilesky LJ, Garfield CF, Barnett JC, Cohn DE. Economic impact of paclitaxel shortage in patients with newly diagnosed ovarian cancer. *Gynecol Oncol*. 2012;125:631-634.

Printz C. Medication shortages threaten cancer care: the oncology community and the FDA tackle ongoing drug shortage problem. *Cancer*. 2012;118:289-291.