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COMMENTS AND CONTROVERSIES

Chemotherapy Drug Shortages in the United States: Genesis and Potential Solutions

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In October 2011, the US Food and Drug Administration (FDA) announced the end of the cytarabine shortage. Cytarabine is the key chemotherapy drug for the management of leukemia in children and adults, particularly acute myeloid leukemia, and the announcement by the FDA of an end to this 11-month crisis was good news. However, in July 2011, we started experiencing shortages of daunorubicin, another drug critical to the management of leukemia and the second most important drug used to treat acute myeloid leukemia. The daunorubicin shortage has been mitigated somewhat by the fact that it can be replaced with other anthracylines, albeit with different toxicity profiles. However, daunorubicin is an essential component of clinical trial protocols for leukemia in the United States, and its shortage has created serious challenges in conducting leukemia research.

Cytarabine Shortages: The Trigger for Heightened Awareness

First noted in December 2010, the cytarabine shortage entered public consciousness this spring with several reports in mainstream media about increasing shortages of chemotherapy drugs and their impact on thousands of patients with cancer. Chemotherapy shortages have included, at various times, doxorubicin, cisplatin, paclitaxel, etoposide, mechlorethamine, daunorubicin, cytarabine, fluorouracil, leucovorin, and many others. The shortages are not unique to chemotherapy agents but occur across a broad range of medicines. Chemotherapy drug shortages are generally more critical because of the lack of equivalent alternatives for most agents. Shortages seem to be most sharply felt in the United States, but they are a global phenomenon that exists in varying degrees around the world. They have grown at an alarming rate in the past 2 to 3 years and have tripled in the past 5 years.[1] Five years ago, there were 70 drugs in short supply. Today, there are hundreds—and the epidemic seems to be worsening.

In addition to print and broadcast stories over the past few months, this crisis has been brought into focus through work performed by the American Society of Clinical Oncology (ASCO) and others in the medical community. In July 2011, ASCO together with other concerned organizations hosted a briefing for senior congressional staff to raise awareness and explore potential solutions. In September 2011, Charles Penley, MD, chair elect of the ASCO Government Relations Council, testified before the House Energy and Commerce Committee. ASCO has attended FDA meetings on the issue and offered preliminary recommendations on potential mechanisms for mitigating drug shortages. In November 2011, President Obama issued an executive order calling for the FDA to broaden reporting of potential drug shortages, hasten or facilitate the review process to more effectively prevent or respond to shortages, and work with the Department of Justice in cases of possible drug price gouging or stockpiling. This is a step in the right direction, but we should consider other approaches as well.

Contamination and Shortages of Raw Materials and Plant Shutdowns

To address the issue effectively, the root causes of the shortages should be identified. Among the numerous excellent articles published, four describe markedly different causes for the shortages (Table 1).[2-5] Drug companies have pointed to contamination of and shortages in the supply of raw materials and shutdowns of plants by the FDA for quality control issues.[6] In particular, according to the FDA, manufacturing and quality issues account for more than 50% of shortages, with shortages of active pharmaceutical ingredients accounting for only 5% to 10% of the problem.[2-4] As the crisis has escalated, other causes have been highlighted. In Congressional hearings, representatives of generic drug companies have pointed to FDA regulatory complexities and burdensome administrative requirements to recertify manufacturing of generic drugs. Others have cited consolidation within the pharmaceutical industry, resulting in fewer companies willing to produce generic drugs.

Table 1. Cited Reasons for Chemotherapy Drug Shortages

Reason
• 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

Abbreviations: ASP, average sales price; FDA, US Food and Drug Administration.

Market Dynamics

We believe that the unifying mechanism behind the drug shortage can be traced to simple economics. Manufacturers have little incentive to produce drugs with low profit margins and often shift their resources to drugs for which higher profit margins can be anticipated. The vast majority of chemotherapy drug shortages have been in sterile injectable generic agents, most of which are relatively inexpensive to purchase. As described by Chabner,[5] there are a few drug companies (eg, Teva Pharmaceuticals [Petah Tikva, Israel], Bedford Laboratories [Bedford, OH], APP Pharmaceuticals [Schaumburg, IL], Hospira [Lake Forest, IL]) that account for more than 70% of the generic chemotherapy market. With aging plant facilities and limited financial incentives, a breakdown in one manufacturing component might shift the interests and resources of a company to more lucrative products, precipitating a drug shortage. It has been suggested that because of higher profit margins in non-US markets, it is possible some generic drugs are being diverted to foreign markets, thus exacerbating the problem.[5]

Medicare Reimbursement System

Established by the Medicare Modernization Act of 2003, the Medicare formula for reimbursement of physician-administered drugs under Part B was designed to control the rapidly escalating cost of chemotherapy drugs.[7,8] Simply stated, Medicare caps at 6% the amount over the average sales price (ASP) that it will reimburse physicians for drugs used in their practices. Because of the methodology used by Medicare to calculate the ASP, there is a 6-month lag between the time the manufacturers submit their ASP data and when changes in sales prices are reflected in reimbursement. This has the practical effect of making it difficult for manufacturers to raise their prices more than 6% in any 6-month period (because raising the price more than that would cause reimbursement for the drug to be less than the actual selling price) and leaves little flexibility for prices to adapt to free-market supply and demand. The Medicare Modernization Act was implemented in 2005; shortages in chemotherapy drugs began to escalate within a year and have increased dramatically since 2008.

As in most normally functioning free markets, competition among sellers—in this case, generic manufacturers—leads to a decrease in prices. In the case of shortages, the market would be expected to respond with increasing prices. But with regard to chemotherapy, the Medicare payment system has made it difficult to raise prices, creating a situation in which—for low-cost drugs with dwindling profit margins—there is little incentive for continued production.

Although a recent report from the Assistant Secretary for Planning and Evaluation of the US Department of Health and Human Services[9] examining part of this issue did not explicitly conclude that ASP plus 6% was a driving force in shortages, it clearly stated that drugs that have not been in shortage had stable or increasing prices during the period under study, whereas drugs that have gone into shortage almost universally witnessed their prices decrease before the shortage period. Thus, it is possible that the well-intended Medicare rule has had unfortunate and unexpected longer-term consequences that have contributed to the current situation.

In Europe, where there is no such Medicare rule, the prices of generic drugs are higher than in the United States, and the prices of brand drugs are lower (because of agreements between drug companies and governments). This maintains a reasonable profit margin for generic drugs, allowing competition to continue and largely preventing drug shortages.

Gray Market

The shortages have created an opportunity for secondary drug distributors to make additional profits. With early knowledge of potential drug shortages, they have hoarded chemotherapy drugs in anticipation and sold them at amounts 650% to 3,000% of the original prices.[10] This activity is referred to as constituting a gray market and is actually a form of price gouging. The gray market has raised additional concerns about the reliability of drugs being sold to practices, because the pedigree of the drugs is uncertain. There is limited to no ability to trace their chain of custody, nor can we be assured that they have been handled, stored, and transported as required. It is estimated that the gray market accounts for up to 50% of drug sales during a drug shortage.[4]

Financial Pressure Experienced by Oncologists

In a recent opinion piece published in the New England Journal of Medicine, Gatesman et al[4] argue that because Medicare still reimburses oncologists under a buy-and-bill system, there is incentive for oncologists to select higher-priced alternatives as a means for increasing profits. They suggest that faced with the choice of two equally effective drugs—a low-cost generic or higher-cost brand drug—oncologists might choose the latter to increase the margin provided by the Medicare 6% markup, thereby creating a disincentive for the pharmaceutical industry to manufacture generic drugs. We feel that this argument is overly simplistic and does not fully appreciate the complexities of the issue. The fact is that most shortages are occurring in drugs used for diseases for which there is no real treatment alternative (in other words, the oncologist often has no viable alternative to the generic drug). Furthermore, it is important to remember that the intent of the average wholesale price and ASP plus 6% was to allow oncologists to make profits on chemotherapy injectable drugs to cover the practice costs of infusion centers, which are not reimbursed otherwise. This strategy aimed to shift patients out of expensive hospital-based infusion centers and into less expensive practice settings that were also closer to patients' homes and thus more convenient. Overall, the private oncology arm of cancer therapy has been a highly successful endeavor in delivering optimal cancer care in the United States. Reducing the drug margin significantly may lead to a reverse trend (ie, private oncology practices shutting down and/or joining academic or hospital-based practices). This may ultimately reduce access to cancer care in smaller towns and rural areas. It will also discourage current trainees from specializing in medical oncology, thus shrinking the pool of specialists and consequently reducing the quality of cancer care delivery in the United States.

Possible Solutions

Establishment of a pricing floor for generic chemotherapy drugs. The average price of 1 g of cytarabine is \$12 to \$16. The average price of a vial of carboplatin is less than \$5. Under the Medicare reimbursement system, limitations on price increases may mean certain generic drugs will never be profitable enough from a manufacturing perspective. One alternative would be to set a minimum price for generics based on some comparison with a similar brand drug. For example, if a brand drug costs \$50,000 per year, the generic drug may be priced at 5% to 10%, or \$2,000 to \$5,000 per

year. This could provide sufficient incentive for generic drug companies to remain in, or enter, the market.

Mandatory reporting. Legislation introduced by Senators Amy Klobuchar and Bob Casey, and supported by President Obama via executive order, would require that manufacturers provide the FDA with 6 months notice of anticipated drug shortages. Some have worried that this would exacerbate hoarding, either on the part of distributors in preparation for price gouging or hospitals and practices wanting to maintain adequate supply. However, much of the communication that would be mandated would be confidential, allowing the FDA to take steps to mitigate problems without necessarily publicizing this information. Since the issue of drug shortages has gained national attention, the FDA has been the beneficiary of more proactive reporting of shortages and potential shortages from the manufacturers. In 2011, this allowed the FDA to prevent more than double the number of shortages it prevented in 2010.[5] Some have proposed adding a provision to pending legislation requiring manufacturers and/or the FDA to locate alternative supplies within 3 to 6 months of notification of a pending shortage. We think this is worth consideration.

Review of FDA timelines. There is reportedly a backlog of more than 2,000 unapproved generic applications, with a median time to approval of 30 months.[11] It is imperative that the FDA allocate the resources needed to significantly decrease this timeline to approval, thus allowing more entrants into the generic market within the 6-month timeline of the anticipated drug shortage. Apart from the obvious benefit of more timely supply to the market of needed life-saving drugs, the production of adequate capacity would significantly reduce the presence of gray-market players.

Conclusion

There are numerous causes for the escalating drug shortage crisis, but in our view, none are as powerful as simple economics. The most straightforward solution is to change the way generic sterile injectables are reimbursed. As suggested earlier, if the generic drug price is kept at 5% to 10% of the brand drug price, and/or the ASP plus 6% reimbursement is modified to an ASP plus 10% to 20%, the profit margin will remain reasonable, and generic drug companies will have adequate incentive to continue to supply the drug. There may be other approaches to financial incentives that would achieve the same end, and such suggestions would be welcome. Although some experts worry about increasing the cost of care, it should be noted that: first, increasing generic drug prices, which account for 2% of the total cost of chemotherapy drugs, will have a minimal effect on the total cost of cancer care[2,5]; second, the continuing drug shortages may be costing as much as $200 to $300 million per year[12]; third, money can be saved if oncologists have access to reasonably priced generic drugs; fourth, increased costs attributable to the gray market will be eliminated; and fifth, medical errors caused by changing to untested practices will be reduced.

This simple modification in the Medicare rule would hopefully resolve many of the downstream issues. We draw special attention to the gray market and price gouging. These should be investigated at both the state and national levels, and consideration should be given to making these activities explicitly illegal. Finally, the Obama administration should redouble its efforts to streamline regulatory processes so that new applications for generic drugs can complete FDA review within 3 to 6 months of an announced or impending drug shortage. In terms of American lives, a solution to the problem is priceless.

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