Drug Shortages Delay Cancer Clinical Trials

By Merrill Goozner

The mean survival time for people older than 60 years with acute myeloid leukemia (AML) is about 7 months. Only 15% survive 5 years or longer, and that percentage hasn’t changed in decades.

The poor prognosis for these patients is due in part to the fact that many cannot tolerate the toxic chemotherapy used as first-line treatment, a combination of cytarabine and daunorubicin. Both are generic intravenous drugs that have been around since the 1960s, with severe cardiovascular and other side effects. That’s why clinicians were hopeful when a small phase II trial offered preliminary evidence that clofarabine, a less toxic drug that the U.S. Food and Drug Administration approved in 2004 for acute lymphoblastic leukemia in children, had extended life in older AML patients by 3 months.

The Eastern Cooperative Oncology Group launched a major trial to definitively test the comparability or superiority of the less toxic regimen. “Try giving a person over 70 heavy chemo; one in six dies within the first 30 days,” said the Mayo Clinic’s James M. Foran, M.D., principal investigator in a National Cancer Institute–funded phase III trial comparing clofarabine to the standard regimen. The goal is to show that clofarabine has at least comparable, if not better, survival rates.

However, accrual to the planned 747-patient trial, which launched in January 2011, slowed sharply in the first 3 months of this year. It wasn’t because patients feared being randomized to the more toxic arm. Rather, the trial’s 145 sites were plagued by periodic shortages of daunorubicin, one of the two drugs in the comparison arm. Each of the three generic manufacturers that formulate the drug have at various points in the past year informed the FDA that they suspended or curtailed production because of “manufacturing issues,” according to the American Society of Health-System Pharmacists.

The drug shortage dramatically slowed accrual to the trial. The trial enrolled less than 60% of the expected number of patients in the first year, and at least one major site—Memorial Sloan–Kettering Cancer Center in New York—postponed enrollment entirely after the center decided to give priority to pediatric patients for its limited supplies of daunorubicin.

Clinicians who treat the 13,000 patients who get AML each year can substitute idarubicin for daunorubicin in their first-line treatment. But study organizers are wary of changing protocols in the middle of their study to cope with the shortages. “We’re worried that [doing so] might dilute the results,” Foran said. “There’s an on-and-off debate about whether [idarubicin and daunorubicin] are equivalent.”

Increasing Drug Shortage

Although most public concern about sporadic shortages of generic drugs focuses on effects on patients and clinicians in community practice, the shortages are also delaying progress in many clinical trials, especially in oncology. At least 22 drugs on the FDA’s drug shortage list last winter were cancer drugs, and an estimated half of the 400 NCI-funded trials actively recruiting patients had at least one drug on the list, according to the Coalition of Cancer Cooperative Groups.

One of the groups most heavily affected, the Cancer and Leukemia Group B, has issued eight shortage notices involving 23 different protocols for seven different types of cancers between December 2010 and March 2012, according to Richard Schilsky, M.D., past chair of the group who teaches at the University of Chicago. “We’ve had periodic drug shortages for years,” he said. “What’s new is the number of drugs in short supply and how frequently they cycle in and out of supply. One week, you don’t have cisplatin. Two weeks later you have plenty, but etoposide is in short supply.”

In late March, the FDA claimed that “most of the oncology-related drug shortages that are currently listed are resolving.” It offered as examples the increasing supplies of ethiodol, doxorubicin, methotrexate, and thiopeta. The agency also reported that supplies of other commonly used drugs on the shortage list—daunorubicin, vinblastine, cisplatin, doxorubicin, etoposide, 5-fluorouracil, leucovorin, mitomycin, and paclitaxel—“are anticipated to continue to improve over the coming weeks based on the firms’ plans.”

But trial organizers are skeptical that the FDA has come up with an effective strategy for relieving the shortages. Legislation sponsored by Sen. Amy Klobuchar (D-Minn.) and Rep. Diana DeGette (D-Colo.) would codify an executive order that President Obama issued last fall that required companies to notify the FDA when they are experiencing manufacturing or other problems that could lead to shortages. But notification gives the agency few tools to actually relieve the bottlenecks. “I’m not as confident as the FDA,” Foran said. “We were told last August that the supplies would be flowing again, and we haven’t seen it yet.”
Various observers cite many causes for the shortages, including the economics of drug pricing; incentives for oncologists; recent consolidations in the generic drug industry; and, in several cases, the marketing of recently approved branded substitutes for comparable generics (e.g., levoleucovorin for leucovorin). Manufacturers of older, off-patent cancer drugs receive low prices, which the Centers for Medicare and Medicaid Services sets. Their slim profit margin over many years has led to consolidation of the generic drug industry into a few firms with the capacity to produce injectable drugs. These few firms have skimmed on capital investment, observers say, and produce many products from the same lines, often switching between them to minimize inventory carrying costs. When a firm temporarily shuts down because of contamination problems, as several have in the past year, the resulting shortages can affect the entire country. (See J Natl. Cancer Inst. 2012;104(4):264–267.)

To respond to the crisis, the FDA has turned to overseas suppliers in Europe and Canada. But that approach hasn’t worked, either. “These countries are experiencing many of the same shortage issues as the U.S. and for many of the same reasons, including quality problems at large manufacturing facilities,” the agency spokesman said.

**Challenges for Clinical Trials**

That situation leaves clinical trial leaders with an unattractive set of options. “The most common thing is to delay enrolling patients in the protocol,” said Schilsky. “That’s a big problem because it will impact the enrollment. In some trials where there’s an appropriate drug substitution, we can advise swapping out one drug for another drug. But that risks confounding interpretation of the clinical trial.”

The Children’s Oncology Group (COG) faces precisely that dilemma in the proposed 4,450-person trial that began recruiting in February to test clofarabine in at-risk young patients (younger than 30 years) with acute lymphoblastic leukemia. The complicated trial, slated for completion by 2016, has eight experimental and six comparator arms, most of which use at least some chemotherapy drugs in short supply.

“For leukemia, you need to be reasonably confident you have sufficient drugs for induction,” said Peter Adamson, M.D., professor of pediatrics and pharmacology at the University of Pennsylvania and chairman of COG. “You need to have the drug for the first 6 weeks of treatment. If you know your pharmacy is out or will run out within 2 weeks, you can’t put your patient in that study. These patients have to be treated, so they simply don’t get enrolled.”

COG, which enrolls more than 60% of children with cancer in clinical trials, is facing a major dilemma in the dozens of trials already under way. “Once a child is in a study and you hit a drug shortage, you have a protocol deviation you couldn’t know about. You have to document it. Say you’re substituting doxorubicin for daunorubicin. The challenge becomes how you are going to interpret the data. You either put the whole study at risk or you remove all those children from the study, which may move the timeline from 2–3 years to 12 years.”

Experts who have reviewed the underlying economics propose two measures to relieve the shortages: raising prices and encouraging new entrants. The former would require action by the Centers for Medicare and Medicaid Services, which is constrained by broader societal pressures to restrain Medicare spending. To encourage new firms to enter the business, the FDA could expedite its review of generic drug applications. But whether many companies will want to enter the business of producing generic injectable drugs without substantial price increases is unclear.

With little movement on either front, clinical trial leaders can only wait. The Eastern Cooperative Oncology Group’s effort to test a high-dose regimen of bortezomib with several other chemotherapy drugs in patients with multiple myeloma who quickly relapse after stem cell transplantation was essentially put on hold in the first quarter of this year because of doxorubicin shortages. Of the 20,000 patients diagnosed with multiple myeloma each year, about 4,000 receive autologous stem cells via transplantation, and 15% of those relapse early.

The trial, originally scheduled to enroll 45 patients by mid-2011, had enrolled only three patients by the end of March 2012. “We have been effectively on hold since the shortages started,” said Shaji Kumar, M.D., the Mayo Clinic clinician in Scottsdale, Ariz., who serves as principal investigator for the NCI-funded trial. “We managed to complete the treatment in a couple of patients with the available supplies but have not been able to enroll” new patients.

The completion date for collecting data, originally set for April 2011, is still 18–24 months away, he said, even though the trial organizers have amended the protocol to substitute other drugs for doxorubicin. The biggest fear now is that “if it takes too long, other drugs would also become available,” making the data less relevant, Kumar said.