

When Will the U.S. Flinch at Cancer Drug Prices?

High hopes in cancer research are pinned on the targeted therapies—those that aim directly at cancer cells or that cut off a tumor's blood supply without harming healthy tissue. And 2004 was a banner year for such drugs reaching the marketplace; Avastin (bevacizumab), Erbitux (cetuximab), Tarceva (erlotinib), and Iressa (gefitinib) all became available to great fanfare.

With their approval came sticker shock because some of the drugs were priced at thousands of dollars per month of treatment and were only effective as add-ons to other therapies. Clinicians are wondering whether these new cancer treatments—which may, on average, add only a few months of survival—are worth the cost.

“America doesn't want to ask the question,” said Bruce E. Hillner, M.D., of Virginia Commonwealth University in Richmond. “We're not willing to accept limits, so we'll put off that discussion.” Hillner has been doing cost-effectiveness analyses for 15 years. He said the response he usually gets is, “Yes, Dr. Hillner, it's nice of you to call our attention to these issues, but let's not go there.”

“America is starving for effective therapies,” Hillner explained. “We're spending a great deal of money and we're uncertain about the benefits.” Others add that these high costs can only worsen outcome disparities between the haves and the have-nots.

The pharmaceutical companies counter that the drugs are expensive to produce and they add precious time. “It's hard to put a value on extending lives, which these drugs do,” said Nikki Levy, Genentech's manager of corporate relations. She explained that the method used to develop biologicals is a factor in their costs. “Genetically engineered biologic therapies are produced in living cells, which represent extremely complicated manufacturing processes compared to traditional pharmaceutical

compounds,” Levy said. “The average cost of producing proteins through chemical synthesis can be more than 20 times the average cost of producing drugs through chemical synthesis.”

To date, payers, including Medicare, are not refusing to pay and Congress is not pushing hard for reforms.

Colon Cancer Leads the Way

Advanced colon cancer has experienced the most substantial progress. In 2004, two different regimens added about 4–5 months survival beyond standard therapy. FOLFOX (fluorouracil and leucovorin plus oxaliplatin) was found to increase survival by 4.5 months over the standard therapy of IFL (irinotecan, fluorouracil, and leucovorin). A separate phase III clinical trial found that Avastin added to IFL extended survival by 5 months.

Each improvement, however, came with a steep price increase, according to a *New England Journal of Medicine* analysis by Deborah Schrag, M.D., at Memorial Sloan-Kettering Cancer Center in New York. (See box, p. 625.) She estimates that treatment for advanced disease has risen from \$63 for an 8-week course of monthly bolus of fluorouracil plus leucovorin to \$11,889 for 8 weeks of FOLFOX. Adding bevacizumab to FOLFOX almost doubles the price to \$21,033. Erbitux is also approved for advanced colon cancer, though it has not yet shown improved survival. An 8-week course adding the drug to weekly irinotecan costs \$30,790.

Tarceva is approved for patients with non-small-cell lung cancer who have

not responded to other treatments, based on a study in which the epidermal growth factor receptor inhibitor improved survival by 2 months over placebo. Because Tarceva is used as monotherapy in place of chemotherapy, Genentech's Levy said, at \$2000 per month, Tarceva is 50% less expensive than standard chemotherapy and produces fewer side effects that would require their own set of treatments.

Still, the future will likely bring more costly combinations rather than monotherapies. Tarceva and Avastin are being studied together and in combination with other drugs in renal cell, lung, and breast cancers. Iressa, which failed to show a survival benefit as a monotherapy in lung cancer, is being studied in combination with hormonal therapies or radiation in brain and other cancers.

Access to Care

Public hospitals are likely to face the tough cost questions sooner. Otis W. Brawley, M.D., treats cancer patients at Emory University's Winship Cancer Institute and at Grady Hospital, a large public hospital in Atlanta. “I have had to sit down with my pharmacy and therapeutics committee and say, ‘What am I going to not purchase in order to purchase these drugs?’ In our county hospital, we make decisions about employing an additional nurse practitioner or buying a drug for individuals who have a particular disease.”

He used to struggle with the cost of Lupron (leuprolide), a more expensive alternative to orchiectomy for men with prostate cancer. Removal of the testes costs the same as a 1-month supply of the drug. He typically treats his prostate cancer patients with Lupron for 3–4 years. Today Lupron is offered at Grady Hospital, but that wasn't always the case. “Patients were offered orchiectomy or were told, ‘if you can find the money, you can go elsewhere and get this shot rather than lose your testes.’”



Otis Brawley

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He says that public hospitals and private practice oncologists are facing the same dilemmas now with colon cancer patients. FOLFOX is fast becoming the standard of care for metastatic colon cancer, Brawley said, at incredible costs. "Are we going to treat these people with colon cancer or have a hospital that can treat all?"

"Private practice offices, as well, where most people get their chemotherapy, are facing the question a lot," he added. The sting of drug costs promises to worsen with implementation of the Medicare Modernization Act. Chemotherapy drugs infused in physician offices are covered at lower fees than in the past, and even with newly covered fees for drug administration, oncologists expect to bring in less in 2005 and beyond. (See News, Vol. 96, No. 17, p. 1268, "Medicare Cost Containment Strategy Targets Several Oncology Drugs.")

Cost concerns aren't limited to the newest therapies. Clinicians are balking at the cost of Arimidex (anastrozole), although it has shown a disease-free survival advantage over tamoxifen in postmenopausal women with early breast cancer. Generic tamoxifen costs about \$30 per month; Anastrozole, an aromatase inhibitor, can cost \$200 per month. Add to that about \$80 per month for the women taking anastrozole who also need to take bisphosphonates to reduce their risk of osteoporosis.

"You're buying a greater chance of long-term nonrelapse for about 10 times the price of tamoxifen, for less than 5% of patients," Brawley said. "It's a huge question mark. We are very selectively using Arimidex for women at very high risk of relapse. The majority who get adjuvant therapy get tamoxifen. However, as the community standards move more and more toward Arimidex, we are going to have pressure to go spend that increased money on Arimidex."

Societal Costs

As health systems make their decisions about the care they can offer, cost-effectiveness studies are done to help society make appropriate choices. An analysis of the Arimidex data stated

the incremental cost-effectiveness ratio fell well within the range of acceptable (see News, Vol. 97, No. 2, p. 86, "Anastrozole Data Show Continued Delay in Relapse, But No Clear Survival Advantage").

These types of cost-effectiveness analyses are rare. "The unfortunate part is that 80% to 90% of clinical trials don't have these studies built in," Hillner said. He added that there is a sense among practitioners and advocates, "why do I have to show cost effectiveness if it works?"

With Schrag, Hillner and other colleagues projected the cost-effectiveness of FOLFOX versus IFL as first-line therapy for metastatic colorectal cancer using data from a Mayo Clinic study that showed the overall survival advantage of FOLFOX.

The new intervention proved expensive, averaging \$80,000 per life-year, but the cost was consistent with other interventions widely accepted in oncology. For a survival gain of 4.4 months, the cost per patient was \$29,529. "Some would say that's pretty pricey, and are we as a society acting very rationally?" Hillner noted.

David Satcher, M.D., Ph.D., former U.S. Surgeon General and now at the Morehouse School of Medicine in Atlanta, brought a societal perspective to the table with a recent paper in the *American Journal of Public Health*. "The U.S. health system spends far more on the 'technology' of care (e.g., drugs, devices) than on achieving equity in its delivery. For 1991 to 2000, medical advances averted 176,633

deaths, but equalizing the mortality rates of whites and African Americans would have averted 886,202 deaths. Achieving equity may do more for health than perfecting the technology of care."

So far, the only people being publicly vocal about drug costs are a handful of health care leaders. Payers aren't denying coverage in any major way. Congress has prohibited Medicare from negotiating better prices with drug companies. In addition, several oral cancer drugs—including Avastin, Iressa, and Tarceva—are covered under a 1-year Medicare demonstration project. (See News, Vol. 97, No. 1, p. 6, "Medicare Demonstration Projects Acknowledge Evidence-Based Medicine in Cancer Care.")

In a *Washington Post* editorial, Robert E. Wittes, M.D., physician in chief at Memorial Sloan-Kettering Cancer Center, called for government price controls "if the industry fails to come to its senses quickly."

Other governments have been in the business of limiting care based on cost. The Australian government's Pharmaceutical Benefits Advisory Committee determines which drugs are made available as a pharmaceutical benefit, based on benefit and financial cost. The United Kingdom relies on the National Institute for Health and Clinical Excellence (NICE) for such advice. Canada has a similar system.

A 2005 poll by the Kaiser Family Foundation says the U.S. public is not happy with the overall rise in drug prices. Close to two-thirds (65%) of

Rising Costs of Chemotherapy

Last year, Deborah Schrag, M.D., wrote an editorial in *the New England Journal of Medicine* that raised concerns about the rising costs of the newer targeted chemotherapy drugs. Using the May 2004 average wholesale price of chemotherapy drugs, she estimated the costs of different regimens for 8 weeks of treatment for metastatic colorectal cancer:

Regimen	Drug Costs (\$)
Monthly bolus of fluorouracil plus leucovorin	63
Irinotecan alone	9,497
Weekly bolus of fluorouracil plus irinotecan (IFL)	9,539
Leucovorin and fluorouracil plus oxaliplatin (FOLFOX)	11,889
FOLFOX with biweekly bevacizumab	21,033
Weekly irinotecan plus cetuximab	30,790

Source: N Engl J Med 2004;351:317-19.

respondents said there should be more government regulation of prescription drug prices; 70% of those people support more regulation, even if it leads to less research and development of new drugs.

Wittes and Hillner don't hold much hope for fast changes. Wittes

predicted that nothing will happen until patients start yelling when they are denied treatment or have to mortgage their homes to get it.

"Given that we haven't pushed back as a community in 15 years, I don't

see things radically changing in the next 3 to 5 years," Hillner said. He predicts that it will have to happen in another disease first, such as cardiovascular disease. "I don't think oncology is going to lead the charge."

—**Cori Vanchieri**