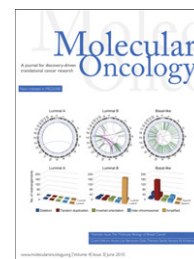


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## News & Views

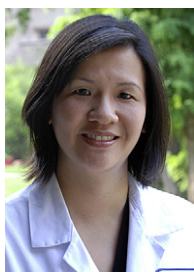
# The cost of hope: Doctors weigh the benefits of new drugs against sky-high costs

*Samuel Loewenberg*

As much training as a physician has in the complexities and nuances of a disease like cancer, nothing can prepare them for the labyrinthine rules and twisted economics that occur at the hazy crossroads where pharmaceutical manufacturers and insurance companies meet. Nowhere is this more true than in America, which is the world's most important single market for drugs, as well as it's most expensive.

The new class of gene-specific drugs which have revolutionized oncology over the last decade have not only changed the way doctors practice medicine, they have filled the coffers of drug companies. Yet the extent to which these new breed of oncology medicines actually help patients varies dramatically, and many people question whether the costs are justified by the benefits.

"These drugs are very very expensive, there's no doubt about it," said Dr. Yu-Ning Wong of the Fox Chase Cancer Center in Philadelphia, who has researched how the cost of drugs has influenced patient use. Because the drugs work differently in different subsets of patients, depending on the disease and clinical situation, "it is hard to put a value on the drugs in just one specific context," she said. A recent study, which she co-authored, concluded that "Whether the benefits are worth the costs clearly depends on the stakeholder; patients with advanced cancer may perceive greater value than healthy patients, policymakers, insurers, and physicians."



Dr. Yu-Ning Wong

Either way, for drug companies, oncology drugs have become a new path to massive profits. Genetic mapping has opened up new areas for research, and pharmaceutical companies have jumped at the opportunity. It makes not only scientific sense, but also market sense. Cancer drugs, which previously have been in short supply, are especially attractive from a financial perspective, because of the premium prices drug companies can charge, which in the U.S. may go to more than \$90,000 per treatment. Such sky-high prices mean that drug companies earn huge profits from drugs even if they have limited effectiveness or are only used for rare types of cancer. GlaxoSmithKline reportedly charges \$98,000 for a six-month treatment of the drug Arzerra, used for chronic lymphocytic leukemia, which affects 15,000 Americans per year. A new drug which to treat peripheral T-cell lymphoma, called Foltyn, is to be priced at \$30,000 a month, while Clolar, for pediatric leukemia, reportedly costs \$34,000 a week.

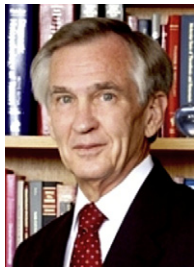
The gargantuan returns means that research on oncology drugs is at an all time high. There are some 860 oncology drugs either in clinical trials or awaiting FDA review, which is almost double the amount in development for infectious diseases like AIDS, malaria, and tuberculosis, according to the Pharmaceutical Research and Manufacturers of America, the drug industry's trade and lobbying organization. In 2009, the cancer drugs in development included 129 for leukemia, 122 for lung cancer, 106 for breast cancer, 99 for lymphomas, 61 for brain cancer and 203 for solid tumors.

By 2008, cancer drugs accounted for 23 of the top 200 biggest selling drugs in the world, more than double what it was a decade before, according to statistics from the magazine Med Ad News. Twenty cancer drugs had over \$1 billion in sales, and are now the biggest single category of worldwide drug sales.

Oncology drugs only became appealing to big pharmaceutical companies in the last decade or so with the introduction of drugs such as Avastin and Herceptin, heralding the start of biologic directed therapy.

"It has clearly changed the profession from both a clinical and research perspective," said Dr. Edward J. Benz Jr.,

President of the Dana-Farber Cancer Institute at Harvard University. Doctors now need to target a therapy to the particular subtype of tumor which will best respond. “It has really changed the way we approach treatment. We try to match therapy with as individualized profile of a patient as we can.”



**Dr. Edward J. Benz Jr.**

“The holy grail in cancer is better understanding how to target the drugs and who they will be the most effective in,” said Dr. Wong. “We are trying to focus on the patients who will respond best to these medications.”

When it comes to cancer, the traditional blockbuster method of producing a super drug, such as the cholesterol-lowering drug Lipitor, that helps millions of patients, does not seem to apply. Rather, in the new era of personalized medicine, specific genetic information from a patient’s tumor is used to help identify which anti-neoplastic agents may specifically benefit the individual, has meant the introduction of new specialized types of treatment. This type of bespoke medical treatment comes at a high price.

The drugs are for the most part unique, so they are not easily substituted for cheaper alternatives, as in most other types of medicines. In the past, drug companies thought of oncology as a poor market: the many types of distinct cancers, which affect only a limited pool of patients, and the high mortality rates, meant that only a relatively small group would use the drugs, and not for very long – which is a hard sell to market conscious executives. After all, it was creating drugs for the massive market of life-long users, such as for cardiovascular and lifestyle drugs, which have made pharmaceutical companies one of the world’s most profitable industries.

“It is all the dollars”, said Dr. Lee Newcomer, the Senior Vice President of Oncology for UnitedHealthcare, one of America’s largest insurance companies. Drugs have a very high reimbursement potential, he said, and like any business, they are going after the biggest return.

The world’s largest drug company, Pfizer, is taking a major bet on oncology, devoting about 20 percent of its research budget to developing drugs in that area, according to *The New York Times*. As part of its new cancer strategy, Pfizer has a research complex set up on the cliffs south of Los Angeles with over 1000 scientists dedicated to developing new medicines. Pfizer has projected sales of cancer drugs at \$11 billion by 2018, which will be more than four times its 2008 sales. The hope is that cancer drug profits will replace the billions it will lose after Lipitor, the biggest selling drug in the world, ceases to be patent-protected next year.

“I’ve taken a lot of personal interest in this business unit,” Jeffrey B. Kindler, Pfizer’s chief executive, told *The Times*. “We think we are positioned to be a top leader in oncology.”



**Dr. Lee Newcomer**

Dr. Newcomer believes that the FDA has approved many oncology drugs, despite sometimes having evidence of scant benefits, in part because of pressure from patient groups. He notes that drugs which may only extend life by relatively small amounts are getting approval, such as the recent certification of a drug for pancreatic cancer which had only a 10-day improvement in survival rates. Or one of the biggest selling drugs, Avastin, which when used for breast cancers causes tumors to shrink, but does not, on average, prolong life.

It is only recently that doctors are beginning to focus not just on whether the drug is having the desired effect, such as shrinking the tumor, but also whether that results in longer life expectancy. This is particularly an issue in drugs that treat pancreatic and breast cancer. “We need to look at increased overall survival rates,” said Dr. Dan Sullivan, the associate center director for clinical investigation at The H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida.

So far, most cancer drugs are not in the same class as best-selling medicines such as the cholesterol-lowering drug Lipitor, which is considered to be an extremely successful life saving



**Dr. Dan Sullivan**

drug. But a patient stricken with cancer is often looking for any solution, at any price, even when the drugs available are not likely to prolong life for more than a few months. Drug industry critics also note that while drugs are expensive to develop, the cost set by pharmaceutical companies is not based on the actual cost to research and manufacture them, but is simply a reflection of what the companies believe the market will bear.

Dr. Newcomer notes that the cost of cancer therapy has been increasing at about 15 percent a year, compared with overall medical care at 8 percent, and wages at 3. Companies can charge anything they want, “because the insurer is forced to pay for it,” he said. Without some kind of price controls, “we are in a very dangerous situation in terms of breaking the bank,” said Dr. Newcomer.

It is not surprising that insurance companies complain that they are captive to drug companies, since they almost

always have to pay for a drug once it has been approved by regulators. The companies say that high drug prices are passed on to consumers in their insurance payments. This is true, but it is not necessarily given that patients should bear the cost. The insurance companies, in fact, would appear to be able to pay for the costs of innovative treatments: after all, the top five U.S. insurers, which included UnitedHealth Group, had a profit of 12.2 billion in 2009 – a 56 percent increase from the previous year.

While the insurers continue to squabble with drug makers, oncologists are busy trying to figure out how to best use these new drugs. The struggle in oncology now is figuring out which drugs will work with the subset of patients whose genetic profiles suggest they will benefit. To that end, cancer centers work closely with pharmaceutical companies in setting up elaborate clinical trials to see what drugs are the most effective with which patients. The H. Lee Moffitt Cancer Center and Research Institute, for instance, has a partnership with Merck and Co. Inc., to collect tumor tissues and clinical data so they can ultimately identify gene expression profiles in the tumors that may predict responses to specific drugs. They have signed up 50,000 patients at the Moffitt Cancer Center and its affiliate institutions in Florida and six other states, from whom they have taken tumor tissue from 15,000, and performed gene expression profiling on 10,000 samples. This large database offers the opportunity for mining the data in such a way that the researchers hope to find which drugs will be most effective with subsets of patients.

“I’m encouraged that pharmaceutical companies are doing this,” said Dr. Dan Sullivan, the associate director of clinical investigation at Moffitt. Because of the “astronomical” cost of developing new drugs, it is fortunate that drug companies are now focusing on oncology, said Dr. Sullivan. “There’s a lot of opportunity for impact.”

At present, though, there are also many hurdles. Simply put, doctors do not yet know what aspects of tumors cause certain drugs to work better than others, or not at all. Things become even more complicated when combination therapies are introduced. So far, the project of sub-classifying tumors by using molecular markers is still in its infancy.

One of the biggest obstacles to effective and safe drug use is getting enough patients into clinical trials, which at four percent in the U.S. is far lower in cancer than in many other common diseases. “There are not enough patients enrolling in the clinical trials that are going on,” said Dr. Benz.

Finding enough patients to test out a drug thus becomes increasingly difficult, because the numbers are relatively scarce. In lung cancer, for instance, researchers and clinicians are now focusing their efforts on a mutation in a gene called ALK (anaplastic lymphoma kinase), which comprises only three percent of lung cancer patients. One solution to this is doing clinical trials spread across many different research institutions, said Dr. Benz.

“Now it is a blunt instrument. Right now we have too few targets. We have only a handful of examples where that classification at a molecular level can really be used to predict therapy,” including certain subtypes of sarcomas, breast, lung, and colon cancer, said Dr. Benz.

One major conundrum, where cost and research meet, said Dr. Benz, is that “the more precise you are in matching the right drug to the right patient, the smaller the market gets... so the cost of developing that drug gets spread over a smaller number of patients.” He is worried that drug companies will not want to develop more precisely targeted drugs because of the fear that they make a huge investment and which will be of use in only a small percentage of patients.

The solution to this will be researching ways to understand how a drug could work on aspects of a tumor that are common across different types of cancer. Researchers must begin thinking about cancers not just by the body part in which they are located, but by finding common genetic components that may be similar across seemingly different types of cancers. In many cases, a type of tumor in one part of the body might work in another tumor somewhere else.

For purposes of clinical research, oncology scientists should reclassify tumors to focus more on the genetic components rather than on the location in the body where it arises, said Dr. Benz. “You have to look at it from a genetic perspective and be somewhat agnostic about what the body part is,” he said. For other aspects of treatment, however, the physical location of the tumor will continue to be one of the crucial factors in any treatment regimen.

One area of concern is that with the increase in cancer drugs, patients frequently request experimental drugs, which they may have heard about from the internet or cancer support groups (which in many cases receive funding from pharmaceutical companies).

“There’s a danger,” if patients are given an experimental drug without sufficient study about the drug’s side effects, said Dr. Sullivan. “A lot of these drugs have significant side effects that sometimes don’t turn up until they are in later trials,” including cardiac, pulmonary, or vascular problems that are potentially fatal, he said.

Insurance companies frown on experimentation; doctors have to make the case that there is a good clinical trial to support off-label use, said Dr. Newcomer. “Personalized medicine doesn’t mean that you no longer have to pay attention to evidence,” he said. UnitedHealthcare will support off-label uses recommended by The National Comprehensive Cancer Network, an alliance of leading cancer centers that researches effectiveness and safety.

Many patients are desperate for a cure, and oncologists, with little clinical evidence to work with, may sometime give a drug to a patient without a sufficient base of research, said Dr. Newcomer. “It’s nothing more than spitting in the wind, you don’t know that it is going to work, and I would argue, dangerous,” he said. Dr. Newcomer pointed to the case of Xeloda, citing a study that found that women over the age of 65 who received the drug were twice as likely to die or suffer a relapse as those that received standard chemotherapy.

Progress could be made in lowering the costs of clinical trials, streamlining regulations, and using more precise targeting of patients who might benefit, said Dr. Benz. In particular, he pointed to the need to allow clinical trials on combination therapies, which in practice are often the most effective. But regulatory prohibitions on testing multiple drugs at once, as well as pharmaceutical companies’ concerns about exclusivity, mean that this often does not happen.