Cancer Drugs: Weighing the Risks and Benefits

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Few deliberations have greater bearing on human health than when the Food and Drug Administration weighs the risks and benefits of drugs designed to treat life-threatening diseases, such as cancer. FDA physicians who specialize in treating cancer (oncologists), chemists, statisticians, microbiologists, pharmacologists, immunologists, and other experts work in concert to evaluate cancer drug data, weigh the risks and benefits, and reach a decision to approve or not approve. If the scale is tipped on the side of benefits, the drug is approved and allowed on the U.S. market. Patients, doctors, caregivers, and family members must also weigh the risks and benefits of drugs to decide which treatments to use.

Cancer is the second most common cause of death in the United States, according to the American Cancer Society, exceeded only by heart disease. Thirty years ago, half of the Americans diagnosed with cancer died from the disease within five years. Today, the five-year survival rate is up to 65 percent, credited to advances in diagnosing cancers at an earlier stage and the development of more effective treatments.

The burgeoning research area of cancer drug development and an accelerated drug review process have produced many more treatment options. Over the last decade, the FDA has approved 43 new cancer drugs, compared with 27 during the previous decade.

Cancer Drug Review Process

Cancer drugs are regulated by the FDA under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. Under the acts, the FDA may approve a new drug for marketing in the United States if it is supported by substantial evidence of safety and effectiveness demonstrated in adequate and well-controlled studies. The drug’s manufacturer or marketer must show this evidence by submitting an application to the FDA that includes results from studies of the drug’s use in people (clinical trials).

FDA oncologists and other agency experts review cancer drug applications and evaluate the study results. When seeking outside advice regarding drug approval or drug labeling, the FDA calls upon the expertise of a group of leading cancer specialists, clinical practitioners, and patient representatives who make up the FDA’s Oncologic Drugs Advisory Committee (ODAC).

At an ODAC meeting, the pharmaceutical company presents findings from clinical trials on safety and effectiveness of the drug, and FDA staff present their assessments after reviewing the drug application, which includes extensive documentation about the drug’s chemistry, its proposed use for one or more specific purposes, and data from clinical trials. The ODAC carefully considers the presentations and votes on questions posed by the FDA intended to guide the
agency in its decision to approve or not approve the drug for marketing or for a
new claim.

**Cancer Clinical Trials**

Clinical trials for cancer drugs are somewhat different from those for drugs used
to treat illnesses that are less serious. For a less severe disease or condition, the
commercial sponsor may show that the drug works better than an inactive
substance (placebo), but generally does not have to show that it works as well or
better than other drugs on the market to treat the same illness.

Studies involving cancer drugs usually do not use placebos, says Patricia
Cortazar, M.D., an oncologist in the FDA's Office of Oncology Drug Products.
"Because cancer is a life-threatening illness, it would not be ethical to give
placebo when something better than placebo is available." In cancer trials, a new
drug is usually compared to a drug or a combination of drugs that are commonly
accepted and widely used to treat the same type of cancer, known as the
standard of care, or standard treatment.

"The standard of care changes over time as new drugs or drug combinations that
are shown to be better become available," says Cortazar.

The FDA may approve a drug for several uses (indications). If a drug is approved
for one indication, it must still be shown in clinical trials to be safe and effective
before the FDA will approve it for another indication.

For example, the drug Erbitux (cetuximab) was approved in 2004 to treat colon or
rectal (colorectal) cancer that had spread to other parts of the body
(metastasized). In 2006, Erbitux was approved to treat patients with head and
neck cancer whose cancer is inoperable. To support a claim to treat colorectal
cancer, Erbitux's manufacturer, New York-based ImClone Systems Inc,
presented evidence that the drug, when given with another chemotherapy drug
(irinotecan), caused tumor shrinkage in 23 percent of the colorectal cancer
patients whose tumors were previously growing with irinotecan alone. For head
and neck cancer, ImClone showed in clinical trials that the drug, along with
radiation treatment, extended patients' lives for 20 months longer than with
radiation treatment alone.

Recently, a pharmaceutical company requested that the FDA approve its drug for
a second indication without conducting additional clinical trials to show an effect
on cancer in this new indication. The FDA had originally approved the drug
Abraxane (paclitaxel protein-bound particles) in January 2005 for advanced
(metastatic) breast cancer that had not responded to other treatments in clinical
trials.

In 2006, Abraxane's manufacturer, Abraxis BioScience Inc. of Schaumburg,
Illinois, submitted a drug development proposal, instead of an application, for
approval of Abraxane to be used in combination with chemotherapy for the
indication of adjuvant treatment for breast cancer. Adjuvant treatment is a
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therapy given after the main treatment to lower the chance of a cancer coming back. Abraxis proposed conducting a 30-patient study looking only at the drug's side effects instead of a large randomized clinical trial to show safety and effectiveness of the drug. In a randomized clinical trial, participants are assigned by chance to separate groups that compare different treatments. Neither the researchers nor the participants can choose which group, so the treatments can be compared objectively. The FDA usually requires randomized clinical trials for diseases that affect a large number of people.

Abraxis argued that the drug had already been approved for metastatic breast cancer based on randomized clinical trials that compared it to the standard of care, Taxol. Abraxis stated that its drug contained the same active ingredient as Taxol, a cancer drug approved both for metastatic breast cancer and for adjuvant treatment for breast cancer, the indication for which Abraxis was seeking approval. Taxol's approval as adjuvant treatment for breast cancer was based on the results of a randomized trial of more than 3,000 patients.

Before the FDA's ODAC on Sept. 7, 2006, Abraxis stated that a trial for effectiveness was "not scientifically necessary and would significantly delay the approval" and that "Abraxane consistently demonstrated antitumor activity that was superior to Taxol in patients with metastatic breast cancer, and there is no scientific reason to believe that Abraxane would be less effective than Taxol" as adjuvant treatment for breast cancer.

The FDA told the ODAC that Taxol and Abraxane were distinctly different. "The two drugs have different formulations and different infusion rates," said Richard Pazdur, M.D., director of the FDA's Office of Oncology Drug Products. "They have different toxicity profiles. Large randomized trials provide important information to patients in making decisions regarding which drug they should take."

Adjuvant treatments for cancer are designed to potentially cure people at risk for disease recurrence, says Cortazar. Toxic side effects that may be acceptable to treat advanced cancer, where a person is more likely to die from the disease, may not be acceptable for adjuvant treatment. The advisory committee recommended by a vote of 13-1 that the FDA not approve Abraxane as adjuvant treatment for breast cancer without randomized clinical trials, and the FDA concurred.

**Evaluating Safely and Effectiveness**

A cancer drug may be considered effective if it extends a person's life (survival). increases the probability that a person will remain alive without the disease getting worse (progression-free survival). shrinks the tumor (response rate), or relieves other symptoms. In short, FDA cancer drug reviewers ask, "Does the drug prolong life, control the disease, or relieve symptoms1 And does the scientific evidence support it?"
These benefits are weighed against the risks of the drug. No drug is absolutely safe—all have some risks, or potential side effects. "Safe" means that the benefits of the drug outweigh the risks for its intended use in the population the drug is intended to treat.

Cancer drugs often contain potent ingredients that kill cancer cells. "Unfortunately, most of the drugs used to treat cancer aren't targeted," says Cortazar. "They kill the cancer cells, but at the same time, they kill healthy cells." The death of rapidly dividing healthy cells weakens the body's immune system, putting a person at risk for infections and other health problems. Yet highly toxic effects may be considered acceptable if the benefits are important and the disease is very serious or life-threatening. "With cancer drugs, you accept more toxicity in general than for drugs that are for nonlethal illnesses," says Cortazar, since the effects of cancer can be more damaging than the treatments, and cancer drugs may extend or save lives.

For example, Nexavar (sorafenib tosylate), a drug used to treat adults with advanced kidney cancer, may cause side effects including high blood pressure, heart problems, bleeding problems, rash, diarrhea, mouth sores, and pain, swelling, or blisters on the palms of the hands or soles of the feet. The FDA considered these risks to be tolerable for a drug that had the benefit of delaying tumor growth or death nearly three months longer than in patients who received no anti-cancer therapy in clinical trials, but these risks would not be tolerated in a drug to treat a less serious condition. Nexavar is distributed and marketed by Bayer Pharmaceuticals Corp. of West Haven, Conn.

Numbers Don't Always Count

The FDA does not require a specific number of participants in a clinical trial. but trial size should be tailored to the risks acceptable to people with the disease and in consideration of the rarity of the disease. Similarly, the FDA does not require a specific number of patients to respond to a cancer drug, nor does it require the drug to extend life by a specific number of days so long as the results are convincing and clinically meaningful given the side effects of the drug and other treatment options.

"There is no hard and fast rule," says Edwin Rock, M.D., Ph.D., an oncologist in the FDA's Office of Oncology Drug Products. "The agency looks at data and makes judgments about what's clinically significant and whether, on balance, the benefits exceed the risks." To be considered clinically significant, a finding must show real meaning for patients, such extending their lives or making them feel better.

For a drug to treat a common cancer, such as breast cancer, the agency would expect large clinical trials with hundreds or even thousands of participants. But the FDA would consider a drug for rare cancers tested in a small number of people. The FDA approved Zolinza (vorinostat), made by Merck & Co. Inc. of Whitehouse Station, N.J., in October 2006, based on results of clinical trials conducted in only 100 patients. The drug was approved to treat skin lesions in
cutaneous T-cell lymphoma (CTCL) when the disease persists, gets worse, or comes back after treatment with other medicines. CTCL is a cancer of the T-cells, a type of white blood cell, and patients who have it develop a variety of skin lesions.

It's a rare disease that has only about 1,200 new cases a year in the United States, says Bhupinder Mann, M.B.B.S., an oncologist in the FDA's Office of Oncology Drug Products. "We'd like to have large studies, but it's impractical with certain diseases," says Mann, adding that there are only two other drugs that have been approved to treat CTCL since the late 1990s. Although only 30 percent of the study participants responded to Zolinza, "you put it in context of rarity of the disease and what is currently available," says Mann.

The FDA may approve a use for a drug if the drug shows evidence that people live longer or live without the disease getting worse for a certain period of time, even if it's just a few weeks or a few months. For example, the FDA approved Vectibix (panitumumab), manufactured by Amgen Inc. of Thousand Oaks, Calif., in September 2006, for use in people with colorectal cancer that has spread to other parts of the body and whose tumors were no longer responding to any standard chemotherapy. In clinical trials, people who took the drug, on average, had a growing tumor or died 96 days later—33 days longer than in people who received only treatment of symptoms (supportive care).

Physical Evidence

In addition to evaluating data from clinical trials, the FDA may look at X-rays, computed tomography (CT) scans, or even photographs that a pharmaceutical company provides to establish whether a drug is truly effective. For the review of Zolinza, the agency had asked Merck to submit before-and-after photographs of skin lesions.

"In some of the photographs, improvement is easy to see, but in others, it is difficult to evaluate," says Mann. The raised surface of a skin lesion may be evident to the touch, but not easily distinguishable in a photograph.

The photographs were considered to be supporting evidence to help assess the benefit of the drug, says Mann. The pharmaceutical company was also required to submit measurements of the lesions and classification of their severity.

Weighing the Risks and Benefits as a Patient

The FDA weighs risks and benefits of a drug in its decision-making as a regulatory agency. But every person diagnosed with cancer, in discussions with his or her doctor, must also weigh benefits and risks before making treatment decisions as a cancer patient.

These decisions can be very difficult, especially when a person is first diagnosed, says Patty Delaney, director of the Cancer Liaison Program in the FDA's Office of
Special Health Issues, and two-time cancer survivor. "You walk into the doctor's office, and you may feel fine—you walk out and you're devastated." With some cancers, she says, "you then start the slow degradation into feeling absolutely horrible. You then slowly come to terms with your diagnosis and begin to hope that maybe you will get better—but you also know that the disease may kill you. It's terrifying."

Patients who don't respond to the standard-of-care treatments also are faced with hard decisions, says Delaney. "Sometimes there's not very strong data in the literature on what to do. The doctor asks the patient what he or she wants to do, and the patient doesn't know what to choose, she says. "People want to be in a partnership with their doctor, but they're often left with making a hard choice with little information."

"You can have your doctor choose for you," adds Delaney. "There is nothing wrong with that."

Philip Rosoff, M.D., agrees. "People have different ways of grappling with a situation when they have lost control," says Rosoff, an associate professor of pediatric hematology-oncology at Duke University School of Medicine and director of the Duke Hospital Clinical Ethics Program in Durham, N.C. "When they're faced with something like cancer, some people think that they do have control and want to run things. But for most, their universe is upended. Most want to be told what to do-they find it very comforting."

Rosoff notes an emphasis in society on autonomous decision-making that doctors are often afraid of impinging upon. "We've abandoned our roles as advisors and healers. We give patients this smorgasbord of options: A, B, C, and D—then ask, what do you want to do? Instead of giving A, B, C, and D, and saying, 'this is what I would do.' We do a disservice to patients when we don't use our expertise to give advice and to make recommendations to them."

When a number of treatments have been tried and failed and the person is dying, doctors may discourage further treatment, says Delaney, but patients don't want to run out of options. "Most don't want to hear that they aren't going to get treatments. Some of these drugs are like atom bombs going off in front of you, but a patient is often willing to take many more risks. People have a survival instinct. The mindset of people with cancer is, 'just give me anything and everything."

"But lately, some patients and families are stopping treatment because they are beginning to question the advisability of continuing drug treatment when death is imminent," says Delaney. "And now, with the cost of cancer drugs rising precipitously, patients and families are asking if continued treatment is affordable when we do not know whether it will add to a patient's life."

David Kelly did not want to stop treatment. He had a very strong survival instinct, and he underwent numerous toxic treatments and surgeries for his cancer,
according to his fiancee, Patricia Davis, of Greenbelt, Md. In January 2004, 59-year-old Kelly was diagnosed with "metastatic carcinoma of unknown origin.

"At the first appointment, we were told it was in the liver and it was stage 4 cancer," says Davis. The doctors told Kelly his chances were less than 1 percent that they could completely rid his body of cancer and less than 5 percent that it would go into remission and, if it did, it would come back.

"Dave said, 'I'm not ready to die—I want to fight this:' says Davis.

The doctors were very good about laying it all out, Davis says, adding that they informed them of serious risks, such as blood clots and heart failure, in addition to providing information sheets and brochures outlining the treatments and risks. Despite the risks, "Dave was willing to try anything to eradicate the cancer." Over 18 months of treatment, Kelly had several courses of chemotherapy infusions in the hospital, numerous oral medications to take at home, three back surgeries when the cancer spread to the spine, and a partial hip replacement when it spread to the pelvis.

As cancer cells multiply and spread to the bone, the pain is said to be excruciating. "The only way to alleviate the pain was to operate:" says Davis, adding that the surgeon cut out some of the cancer and bone, then reconstructed the bone and followed up with radiation. "They couldn't cut out all the cancer because it was too close to the spine." After the partial hip replacement, the hospital sent Kelly home in an ambulance when he protested going into a hospice facility. "Even then, Dave said, 'when I get better, I want to come back here and get more treatment:" Davis says. "But at the end, cancer was going through his bones faster than they could operate or radiate." Kelly died in September 2005.

Access to Investigational Cancer Drugs

The FDA recognizes that many patients, like Kelly, run out of options and are willing to risk taking unproven treatments. The agency has put in place a number of regulatory programs and works with manufacturers so that seriously ill patients can get access to promising, but not fully evaluated, products.

Clinical trials. One of the most common methods to get an unapproved drug is to enroll in a clinical trial. More than 10,000 cancer clinical trials are ongoing in the United States. People interested in clinical trials should talk with their doctor, check out available trials at clinica/crill/s.gov, or call the National Cancer Institute's (NCI's) Cancer Information Service at (800) 4-CANCER (422-6237). If a person does not meet the criteria to participate in a clinical trial, usually because he or she has other serious medical conditions, an investigational new drug sponsor can make an exception to treat the patient. The patient's data would not be analyzed with the primary data from the original trial, but would be evaluated separately. Usually, such exceptions occur in the same institutions that are conducting the original trial, where investigators are familiar with the drug.
Single-patient, or emergency, investigational new drug. If enough is known about an investigational drug's side effects and there is some evidence of effectiveness, the FDA may allow a patient to receive a drug in his or her own specifically designed study. Although the FDA's requirements are relatively simple, setting up this kind of access for an individual patient is not, and involves the following:

- The pharmaceutical company must be willing to provide the new drug to the patient. This provision can be expensive and time-consuming for the company since it must track shipments of the drug, create special instructions for its use, and devise a way to collect information on toxic side effects for each patient.
- The study treatment and an informed consent document must be approved by the local institutional review board, a panel of scientists and non-scientists in hospitals and research institutions who ensure the safety and well-being of human subjects involved in research. The patient must give informed consent, understanding that the drug is not approved and may cause known and unknown side effects ranging from mild to fatal.
- The patient's physician must be willing to take responsibility for treating the patient and agree to collect information about the effects of the drug.

Treatment investigational new drug. A promising new drug can be distributed outside of clinical trials under a treatment investigational new drug if

- the drug is intended to treat a serious or immediately life-threatening disease
- there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population
- there is presumptive evidence that the drug may offer some benefit to certain patients
- proper clinical trials are well under way to see whether the drug really does offer patients any benefit.

The FDA cannot force a pharmaceutical company to give an individual patient an investigational drug outside of its planned clinical trials. The drug manufacturer makes the final decision to provide an experimental treatment to a patient. The company may consider many factors, including the amount of information available about the drug, the amount of drug available, and how best to use its resources to optimize development of the drug. In some cases, the company is unwilling to provide the product outside of clinical trials.

Treatment Decisions

The American Cancer Society (ACS) stresses the importance of having frank, open discussions with your cancer care team and getting answers to all your questions to help you understand your specific condition and your options so that you can actively participate in your treatment decisions.
The ACS offers free interactive tools on its Web site to help people with cancer make informed decisions about their treatment. The tools provide details specific to a condition, a breakdown of treatment options and side effects, personalized reports with pros and cons of treatment, and questions to ask the doctor.

**Children and Cancer Drugs**

As with drugs for adults, the FDA weighs the risks and benefits of drugs for children based on clinical trials. "But it’s hard to do clinical trials in children for many drugs—not just cancer drugs—because it's difficult to get a large number of patients enrolled," says Karen Weiss, M.D., pediatric oncologist and deputy director of the FDA's Office of Oncology Drug Products.

Even the most common cancer in children, leukemia, strikes only one-tenth as many children—about 3,200—as adults each year in the United States, according to the NCI.

"Acute leukemia has an 85 percent survival rate, so to show that a new drug improves survival, a sponsor would need a large study and it would take many years," says Weiss.

Sometimes, in lieu of conducting randomized trials in children to demonstrate the effectiveness of a drug, the FDA may extrapolate findings from adult trials of a drug that might also be promising for children. This action may be taken when the disease being treated is similar between adults and children. For example, in 2003, the FDA approved Cleevec (imatinib mesylate) for the treatment of children who have a rare, life-threatening form of leukemia. This approval, the first for a new cancer drug for children in more than a decade, was based on evaluating results from Gleevec-treated adults with the same leukemia together with good responses in a small number of children. As a condition of approval, the manufacturer, Novartis Pharmaceuticals Corp., agreed to conduct pediatric studies after approval to confirm that the drug improves survival or provides other clinical benefits in children. These trials are ongoing.

Because of early diagnosis and successful cancer treatments, about three fourths of children with cancer are cured and able to live into adulthood, according to the NCI. Although the cure rate is encouraging, the recently reported results of a study of survivors of childhood cancer are disturbing. The Childhood Cancer Survivor Study found that survivors appear to have a high rate of chronic health conditions later in life due to organ damage caused by chemotherapy and radiation during cancer treatments. The study tracked more than 10,000 children diagnosed with cancer from 1970 to 1986 and compared their health with the health of 3,000 siblings. The researchers reported in the Oct. 12, 2006, issue of the *New England Journal of Medicine* that 30 years after a diagnosis of cancer, 73 percent of survivors have a chronic health condition, 42 percent have a serious health problem, and 39 percent have multiple conditions.

Doctors and patients need to be aware of the potential for later health problems, says Rossoff, who authored an editorial in the same journal. He emphasizes the
importance of monitoring children who survive cancer as they grow up. "We need to try to convince people they need to be vigilant lifelong." When it comes to treating cancer, Rosoff adds, "A concern about late effects is a luxury of cure. No physician or patient would sacrifice a percentage point of cure for a percentage point of late effects."

Once a medication is approved, the FDA monitors the medication and collects information on side effects including late effects, rare effects, and long-term effects. This postmarketing surveillance program is an important complement to the premarketing assessment because the agency cannot anticipate all possible effects of a drug during clinical trials that precede a drug's approval. Through its continuous monitoring of medical products, the FDA ensures that new safety information is quickly communicated to medical professionals and patients.

For More Information

- Approved cancer drugs: http://www.fda.gov/cder/cancer/
- The NCI's Cancer Information Service (800) 4-CANCER (422-6237) http://cis.nci.nih.gov/