Drug Availability Is an Issue for Cancer Patients, Too

If AIDS activists have done nothing else, they have sensitized the public and the medical research establishment alike to the need to give people with life-threatening diseases faster access to experimental drugs. But AIDS is not unique in this regard. "Many of the issues that have been rediscovered have been important concerns to the cancer institute since the early 1970s," says National Cancer Institute director Samuel Broder.

That does not mean that those issues have been resolved, however. The recent flare-up of a controversy among top cancer researchers over a new drug therapy for colon cancer provides a case in point.

Two clinical trials have indicated that treatment with a combination of the drugs levamisole and 5-fluorouracil can delay or prevent colon cancer recurrences in certain patients who have had their original tumors removed surgically. Having such a therapy would be a major advance, a victory in the "war on cancer," if anyone still thinks in those terms. Colon cancer is the second leading cause of cancer deaths in the developed countries. It will claim an estimated 44,000 lives this year in the United States. And efforts to develop chemotherapeutic regimens to prevent the metastases that take the vast majority of those lives have been unavailing—until now.

So why not help colon cancer patients beat the odds by giving them early access to the levamisole–5-fluorouracil therapy? The main argument, as with AIDS drugs (also see p. 345), centers around the question of when an experimental therapy should be made available to patients with a life-threatening illness. Or in other words, how firmly do safety and efficacy need to be established under those conditions? Charles Moertel of the Mayo Clinic in Rochester, Minnesota, who is the principal investigator on both colon cancer trials, puts the dilemma more starkly.

"Should we continue with sound scientific method or yield to the activists?" Moertel asks. "Scientists are being displayed as sitting in an ivory tower without any compassion. I strongly object to the idea that good science is not compassionate for the patient." He maintains that the levamisole–5-fluorouracil results are not yet firm enough to recommend widespread clinical application of the therapy.

Others disagree—vehemently—with this position. Among these is Vincent DeVita, who was NCI director from 1980 until he left at the end of last year to become Physician-in-Chief of Memorial Sloan-Kettering Cancer Center in New York City. DeVita, who is familiar with the levamisole–5-fluorouracil studies from his NCI days, says, "You could save 12,000 lives per year with this therapy. Why wait?"

At the crux of the dispute is the question of what constitutes a positive result in a cancer drug trial. Moertel holds out for the ultimate "hard" end point—increased survival. The first of the two studies he led, which included a total of 400 patients, indicated that either levamisole alone or the levamisole–5-fluorouracil combination can delay the recurrence of colon cancer and increase survival, especially in patients with "Dukes' C" disease. Such patients, whose tumors have already spread to nearby lymph nodes but not to distant sites in the body, have a poor prognosis. About 75% relapse within 5 years and die.

Although the results of the first colon cancer study were encouraging, Moertel points out that the 15-year history of levamisole cancer trials has been notoriously checkered. "One investigator would do a study and find miraculous things. Another would do a more careful study and find nothing," the Mayo researcher explains.

In any event, a second, more extensive test of levamisole, both alone and with 5-fluorouracil, as a therapy for colon cancer was begun just about 5 years ago, with the last of 1300 participants entering the study in 1986. The patients have not yet been followed long enough, Moertel says, to determine whether the drugs have had any impact on their 5-year survival. Moreover, he notes, the levamisole–5-fluorouracil therapy is too toxic—one patient has died of the side effects—to administer without proof of efficacy.

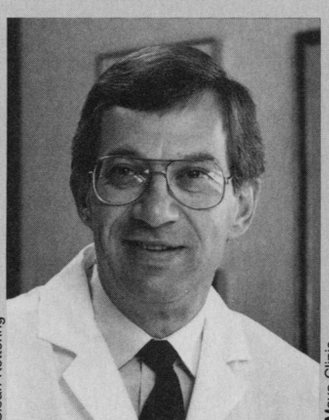
In any large clinical study, however, the data are continuously monitored to see if a treatment is turning out to be either better or worse than expected. And in this case, the monitoring shows that the levamisole–5-fluorouracil combination is having a marked effect in delaying colon cancer recurrences in Dukes' C patients. The effect is so significant, DeVita says, it will certainly be reflected in an increased survival rate when those data are in. By his view, Moertel is being much too conservative.

The Mayo researcher was sufficiently optimistic, however, about the eventual outcome of the levamisole–5-fluorouracil study to suggest to officials of the U.S. Food and Drug Administration and NCI that the therapy be given "group C" status, a step which the FDA took in May of this year. The group C classification, which applies only to cancer drugs, means that physicians can now prescribe the experimental therapy for patients with Dukes' C colon cancer even though it has not yet been approved by the FDA. The levamisole will be available through NCI.

Moertel went to the FDA, he says, because levamisole has not been approved for human use in this country and he wanted to set in motion the regulatory machinery needed to make the drug available should its efficacy be demonstrated. An estimated 25,000 patients would be eligible for the treatment every year in the United States.

DeVita, who 10 years ago was instrumental in moving the FDA to set up the group C designation, would have gone further in this case. He thinks that the NCI should also have issued a "clinical alert" to make physicians aware of the levamisole–5-fluorouracil data and recommend that they consider administering the therapy to their Dukes' C colon cancer patients. "I feel badly that I didn't push the clinical alert before I left NCI," DeVita says.

But Moertel "absolutely" opposes issuing such an alert at this time, and Broder says, "We would not make the data available in a clinical alert without the approval of the clinical investigator." Neither of the colon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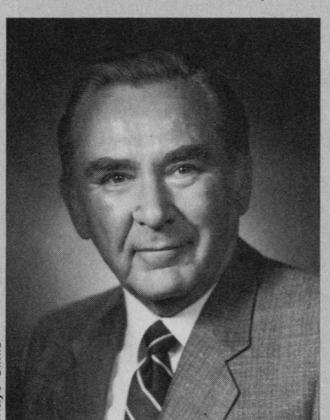
Mayo Clinic

Cancer drug controversy. *Sloan-Kettering's Vincent DeVita (left) thinks a new colon cancer therapy should be made available to patients now. The Mayo Clinic's Charles Moertel disagrees.*

cancer trials has been published, although a report of the first has been accepted by the *Journal of Clinical Oncology*.

The cancer institute has taken another step with regard to the levamisole–5-fluorouracil data, and it touches on an issue, namely the use of placebo controls, that is no less sensitive in cancer research than it is in AIDS research. NCI is now requiring that its grantees tell any colon cancer patient who is considering participating in one of their clinical trials about the promising levamisole results.

The idea is to give them the opportunity to opt for the levamisole–5-fluorouracil treatment, instead of entering a new study, especially if that study is comparing an experimental therapy with an inert placebo. "If it were me I would demand to know all the information, and I would be madder than a hornet if the information hadn't been explained," Broder asserts.

DeVita thinks that placebo controls are no longer justified in colon cancer studies and that any new therapy should be compared to the levamisole–5-fluorouracil combination. He suggests that Moertel is reluctant to announce the results of the levamisole–5-fluorouracil studies because this might interfere with the recruiting of patients for a placebo-controlled trial that he is conducting on another drug combination, Leucovorin and 5-fluorouracil.

Moertel takes strong umbrage at that suggestion. "We're trying to defend that study because we feel it is in the best interest of cancer patients," he maintains. The Leucovorin combination has already proved effective in prolonging the survival of patients with advanced, recurrent colon cancer, and Moertel thinks it may hold even greater promise than the levamisole combination as an adjuvant to colon cancer surgery. In any event, Broder says, the informed consent form for the Leucovorin trial is in compliance with the requirement to inform prospective participants about the levamisole results.

The dispute over the levamisole therapy has a positive side. It carries a strong implication that cancer researchers are at last beginning to make headway against a major killer, even if they do not agree over the current status of the research. Equally apparent, however, is the conclusion that the long-standing issue of when to make experimental drugs available to people with life-threatening illnesses is not likely to be resolved anytime soon. ■ **JEAN L. MARX**

allow greater access to investigational new drugs or INDs—called "Treatment IND"—was judged a failure by Delaney because the staff made little use of it. Delaney charges that the FDA has not delivered on promises made by Commissioner Young.

It was Fauci who gave the latest bureaucratic innovation—the parallel track—its notoriety. He endorsed it publicly on 23 June at a San Francisco meeting on AIDS treatment. (Fauci coordinates a national effort to test new AIDS drugs and talks often with AIDS activists.)

Events added urgency to the proposal. As Fauci, Young, and the AIDS activists were discussing the parallel track this spring, the Bristol-Myers Company revealed that its new compound DDI is less toxic than existing AIDS drugs and is proving reasonably effective for patients in clinical trials (see story this issue, p. 353). AIDS patients will want to use it as soon as possible, which could be in September, if the parallel track is working by then.

Fauci said during the hearing that he recognizes that some AIDS patients could be "disenfranchised" from the benefits of DDI under the traditional research rules. Distribution of the drug would be limited to people in clinical trials, and the trials would randomly give participants either DDI or AZT, an older AIDS drug. The catch is that AZT is quite toxic and has a limited period of usefulness (about 2 years). Patients who have gone beyond that limit, or who cannot take it for other reasons, would be excluded from the trials. Yet, as Eigo and Delaney point out, "AZT-intolerant" people most desperately need the new drug.

Fauci told the committee, as he told his own clinical research chiefs, that "we can be humanitarian and do good science" as well. Mason echoed the sentiment: "We have a responsibility to be compassionate," and the parallel track "might even enhance our ability to get people to participate" in clinical trials.

On the other hand, some researchers worry that the parallel track will be unmanageable. Several who spoke with *Science*—Martin Hirsch of Harvard, Douglas Richman of the University of California at San Diego, and Lawrence Corey of the University of Washington, Seattle—have such concerns. One question is whether the benefits of this new approach will outweigh the risks, even in the short term. Toxic effects not apparent in small Phase I reviews could surface when the drug is distributed on a wider scale, doing unexpected harm. Second, as each new drug appears, there may be a faddish tendency for patients to begin taking it in place of or in addition to those in a clinical trial. Some clinicians say this will make it hard to control the research data.

Finally, because the parallel track will be open to patients who live far from a test clinic, some researchers worry that this geographical exemption will divert patients from major medical centers, adding to the growing problem of recruiting patients for trials.

Similar criticism, though with a different slant, came from Ralph Nader's Health Research Group. Speaking across town on 20 July as a witness before a meeting of the presidential advisory panel on AIDS and cancer drugs, director Sidney Wolfe said the parallel track could create "an extraordinary conflict between researchers and patients." Wolfe and a senior attorney of the group, William Schultz, worry that a fast track plan will jeopardize the conduct of more rigorous clinical trials."Nothing will happen [in validating therapies] if science isn't applied" to the proper testing of an experimental drug, Wolfe said. "The parallel track is fraught with that possibility."

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In addition, Wolfe argues that manufacturers should be required to show that a drug has some efficacy before it is allowed into the parallel track. However, defining a minimal threshold of effectiveness will be difficult. A year ago, many AIDS patients were scrambling to buy dextran sulfate, which had shown biological activity in test tube experiments. The drug was only available in Japan, so AIDS patients formed buying clubs and used a Canadian clearinghouse to purchase it overseas. Scientists soon discovered, however, that dextran sulfate wasn't even absorbed by the body. One way to discourage quack therapies in the future, Wolfe said, would be to prohibit a manufacturer from making a profit on a drug while it is distributed under the fast track system. No guidelines have yet been developed on matters of profit or liability.

Many things remain undefined, and this is what makes the clinic directors so nervous. Richman puts it this way: "People say, here's the concept; we'll fill in the blanks later. But what you put in the blanks will determine whether it succeeds or not."

■ **ELIOT MARSHALL**

With reporting by Marjorie Sun.