Cancer M.D.'s Clash over Interleukin Therapy

Research physicians are engaging in a heated and public debate about a new immunotherapy that some call very promising and others find too toxic to continue

ABOUT a year ago, an immune agent called interleukin-2 (IL-2) made dramatic front-page news as an experimental approach to cancer therapy that sometimes worked for advanced malignancies when all else failed.

Today, this report from the National Cancer Institute is under attack from some quarters as premature and carrying false promise to cancer victims. The side effects are viewed as too severe and the benefits too transient and uncertain.

Even the critics agree that IL-2 and other substances of its ilk, known as lymphokines, may have a future in cancer therapy. But, they add, as originally given, IL-2 therapy should be halted.

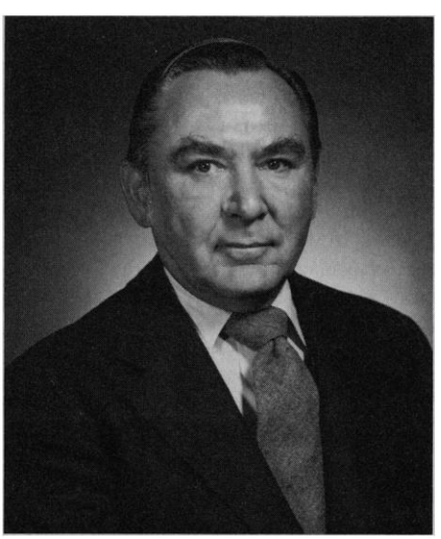
In response, IL-2 enthusiasts argue that the therapy already has become significantly less toxic, that the criticism is outdated, and that survival times are lengthening for certain metastasized cancers treated with IL-2.

It all began when the press widely reported on a paper in the *New England Journal of Medicine** that said 11 of 25 patients with advanced, untreatable tumors had shown improvement. The senior author was surgeon Steven A. Rosenberg of the National Cancer Institute, who had become a minor medical celebrity a few months earlier when he removed a tumor from President Reagan's colon.

A press "update" issued by NCI the day before the *New England Journal* article appeared described the IL-2 experiment as "a new approach to cancer treatment that successfully activates the immune system to destroy cancer cells in patients whose cancers are so far advanced that they no longer respond to chemotherapy or radiation." Although Rosenberg and other NCI officials were repeatedly quoted in the press as saying that the new therapy was preliminary and experimental, the net effect of press reports was to give the impression that a major breakthrough had occurred.

Last month Rosenberg and IL-2 hit the news again, this time when the *Journal of the American Medical Association*† published an article by the NCI physicians, along with an editorial challenging their work and criticizing them bluntly for all the attention it has received from the press. The new Rosenberg paper reports modest success with a modified version of the IL-2 approach he reported a year ago. The initial treatment, in which IL-2 was administered in combination with LAK (lymphokine-activated killer cells), produced "significant" toxicity, Rosenberg acknowledges. The newer study tested IL-2 alone in ten patients; tumors regressed in three of six patients with metastatic melanoma. Toxicity remained significant.

The editorial, by Charles G. Moertel of the Mayo Clinic, calls for a halt to IL-2 studies of the sort Rosenberg and his colleagues have been conducting. "This specific treatment approach would not seem to merit further application in the compassionate management of patients with cancer," Moertel writes, backing up his conclusion with comments about the treatment's toxicity and cost. " . . . [T]reatment with high doses of IL-2 is an awesome experience," he says. "It requires weeks of hospitalization, much of which must be spent in intensive care units if the patient is to survive the devastating toxic reactions." Not all of them have. The treatment causes major fluid retention that can result in fluid in the lungs. It produces fever, confusion, rigors, and often anemia severe enough to require blood transfusions. The dollar costs, Moertel says, reach six figures, and the benefits in terms of long-term remission are not very impressive.



Charles Moertel *of Mayo says IL-2 therapy is too toxic.*

Moertel also attacked Rosenberg and NCI for what Moertel considers publicity seeking. Moertel says his discontent with the handling of the IL-2 work has been festering ever since the *New England Journal* paper came out a year ago. He was particularly galled by Rosenberg's characterization of the work, on the "Today" show, as the "first new kind of approach to cancer in perhaps 20–30 years." And he wasn't happy with an article in the 25 November 1985 issue of *Fortune* that called IL-2 a "breakthrough" on the cover. He did not like the fact that Rosenberg's paper resulted in a cover story in *Newsweek* or that it was reported on all three major networks.

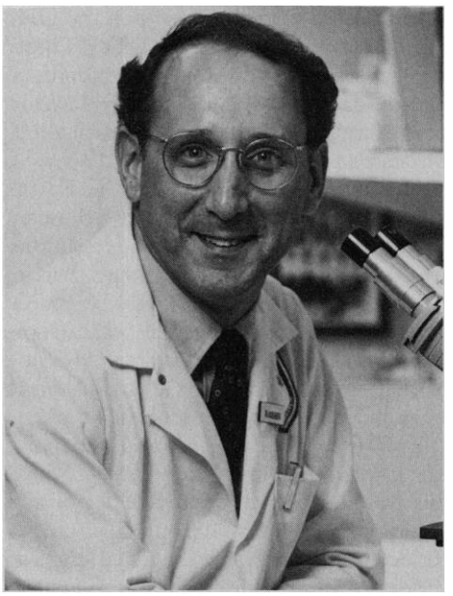
Rosenberg feels stung and angry. He says he disagrees with most of Moertel's editorial, but accepts it as scientific criticism. What he cannot accept is Moertel's allegation that he ever called IL-2 a "breakthrough." The word, he insists, is simply not in his lexicon.

Moertel says he recalls Rosenberg saying the word, but concedes his memory may be playing tricks. In the aftermath of his editorial, he's been unable to find evidence in video tapes. But he adds, the "first new kind of approach to cancer in perhaps 20–30 years" spells "breakthrough" to him.

Rosenberg, however, calls this unfair. He quotes chapter and verse of his writings and utterings that consistently describe IL-2 therapy as preliminary, with no conclusions about therapeutic value. The new approach to cancer, says Rosenberg, was the concept of lymphokines as "adoptive" immunotherapy. And IL-2, he adds, did lead to responses for patients with metastatic disease who had failed to respond to radiotherapy or chemotherapy and were beyond surgery. In fact, says Rosenberg, the press on the whole reported the IL-2 story accurately—though excessively. That excess, he contends, was not due to any NCI promotion, but largely to his own recent prominence as President Reagan's surgeon for colon cancer. It was also due, in part, to the desperation of cancer patients, who hear what they want to hear, says Rosenberg.

But "breakthrough" aside, Rosenberg argues that Moertel's scientific criticisms are out of date. Rosenberg says side effects in the studies, though significant, were not in the "unacceptably severe" ballpark—nor are costs "astronomical." He says the treatment-related toxicity and mortality are less than

N. Engl. J. Med. **313**, 1485 (1985).
†*J. Am. Med. Assoc.* **256**, 3117 (1986).



Steven Rosenberg *of NCI defends IL-2 studies as vital.*

with bone marrow grafts, now considered usual therapy for certain types of cancers.

Rosenberg says Moertel's "major error" was to look at IL-2 as a treatment now ready for wide application. "This should be likened to the early days of surgery, radiotherapy, and chemotherapy, when we were just learning how to use them and they obviously didn't have the benefits they do today," says Rosenberg. "He is misinterpreting this as a final treatment, but it was really a description of a new approach to treatment in the infancy of development."

NCI director Vincent T. DeVita, Jr., likens IL-2's stage of development to vincristine, an effective chemotherapy agent when he was a young NCI investigator in the 1960s. "I would come onto a ward of paralyzed children, because the drug paralyzed the nervous system. They were paralyzed while they were in remission from leukemia. We learned how to use that drug, and now it's given in an outpatient clinic, and kids go out and play afterward."

Furthermore, DeVita notes that Rosenberg and others who are testing IL-2 are devising ways to modify the therapeutic protocols to make subtle but important changes. "You can't make it less toxic if you don't test it," he says. "The idea that we should stop testing because it's too toxic would be to throw away a good therapy. If we had thrown away vincristine in the 1960s, we wouldn't have the cure now for childhood leukemia."

Meanwhile, Rosenberg is itching to talk about his new study of more than 150 patients he just submitted to a journal, presumably the *New England Journal.* Though he will not discuss it until it is published, he says new data justify his previous optimism about IL-2. "We have seen a considerable number of additional responders with less treatment-related mortality than from many accepted treatments for patients with metastatic cancer," says Rosenberg.

But as these leads are pursued, Moertel added in his editorial, "one would also hope that investigators will suppress the urge to publicly state or imply that a breakthrough has taken place until solid evidence exists that, indeed, there has been a breakthrough as the public would interpret it, i.e., treatment that provides either a longer or a better life for the patient with cancer."

To this, Rosenberg states that with 475,000 Americans dying of cancer every year, researchers "can't be too timid, too traditional, or too conservative because the problem is too desperate." ■

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Landsat Commercialization Stumbles Again

Citing undue delays in the release of fiscal year 1987 funding for commercializing the Landsat system, the Earth Observation Satellite Company (EOSAT) of Lanham, Maryland, has terminated all work on the Landsat 6 and 7 spacecraft, effective 5 January 1987. Unless a compromise can be reached, EOSAT's contractors will have to reassign or lay off some 700 workers.

EOSAT, a joint venture of the Hughes Aircraft Company and General Electric's RCA Astro-Space Division, won the Department of Commerce's competition to become the private operator of Landsat in 1985. The company agreed to take over the existing Landsat 4 and 5 satellites and to develop a new generation of satellites, sensors, and ground systems. The federal government, meanwhile, agreed to pay EOSAT a subsidy of some $250 million, spread over 6 years, to aid the company in establishing a commercial market for remote sensing data.

In early 1986, however, pressure from the Gramm-Rudman-Hollings deficit exercise led the White House Office of Management and Budget to delete the fiscal year 1987 installment of EOSAT's subsidy—$69.5 million—from the President's budget request to Congress. In the end, Congress restored $27.5 million of that money and directed the National Oceanic and Atmospheric Administration (NOAA), which had been the government operator of Landsat, to carve out the rest from its other programs. At the same time, the loss of the space shuttle Challenger and the subsequent string of launch failures with expendable rockets left EOSAT's launch plans highly uncertain; Congress accordingly made the payment contingent upon NOAA's submitting a new Landsat commercialization plan for approval of both the House and Senate appropriations committees.

This led to EOSAT's termination notice to its subcontractors. The immediate problem is that Congress has still not approved NOAA's plan, which was submitted in December 1986, and EOSAT has started to run out of development funds. The more serious problem is that NOAA's plan provides for only $209.6 million in total subsidy, instead of the $250 million originally agreed upon, and calls for only one new satellite instead of the original two. (That one satellite, Landsat 6, would be launched in late 1989 aboard a refurbished Titan 2 missile provided by the Air Force.) EOSAT and NOAA are still trying to negotiate an acceptable compromise.

For now, at least, the prospects for a resolution seem reasonably good. The appropriations committees will probably give their approval to the commercialization plan in the very near future, says Thomas Pyke, head of NOAA's satellite and information service. If they do, the fiscal 1987 money will be released and EOSAT's contractors can go back to work with minimal disruption. And as for the changes in the original agreement, he says, "Both sides are still negotiating in good faith." Indeed, he says, the very fact that the White House has agreed to subsidize a one-satellite system is a significant change from last year, when the Office of Management and Budget wanted to cancel the subsidy entirely. EOSAT, however, is still pushing for a two-satellite system.

EOSAT president Charles P. Williams is hopeful that some accommodation can be reached. "We cannot lose sight of the fact that this termination is . . . a blow to the struggling new space commercialization industry in this country," he says. Nonetheless, "We are optimistic that a long-term solution to funding Landsat commercialization is possible." ■

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