READ THE LABEL

FDA PANEL OKAYS CHIRON'S IL-2

WASHINGTON, D.C.—In January the Biological Response Modifiers Advisory Committee (BRMAC) of the U.S. Food and Drug Administration (FDA, Bethesda, MD) cautiously recommended that the agency approve Chiron's (Emeryville, CA) interleukin-2 (IL-2) for treating patients with renal cell carcinoma. Although IL-2 does not "meet the conventional definition of safe and effective," committee members acknowledged that a "small group of patients" could benefit if this potent biologic was made available to them and their doctors. BRMAC members also urged FDA to require "very strong language" describing toxic side effects and limits to effectiveness in any forthcoming IL-2 label information.

BRMAC initially reviewed IL-2 in mid 1990, but made no recommendations about licensing at that time. That neutral encounter between FDA and Cetus (Emeryville, CA), which then was the corporate sponsor for IL-2, proved a blow from which Cetus never fully recovered. Subsequently, neighboring Chiron acquired control of Cetus in a merger-buyout deal and thus became IL-2's sponsor.

A less-combative meeting

The recent BRMAC meeting was less combative than the earlier gathering in 1990. While furnishing the committee with the FDA perspective, Jay Siegel said that the IL-2 database now was better "validated with more patients, more studies, and increased auditing." His tone, comments, and the way he and other agency officials formulated questions for the advisory panel to consider seemed to signal increased confidence in the product. Moreover, Siegel noted, "We now have considerable information on the product: It exists as microaggregates, and they have a considerable impact on pharmacokinetics." Such information, taken together with added clinical experience on dosing regimens, evidently has helped to convince FDA officials that product consistency and quality are also under better control than before.

IL-2 clinical trials have expanded to include 255 patients, compared to 106 at the time of review in 1990. Even as clinical data have accumulated, IL-2 still appears only marginally effective against renal cell carcinoma. However, no other conventional treatment is considered effective against this relatively rare but usually fatal disease, which develops in about 20,000 new patients annually. Average survival for those with this cancer is 6-12 months, and long-term survival is rare once the cancer metastasizes.

IL-2 produced a "significant clinical benefit in a minority of 255 patients" who received the experimental treatment in seven clinical trials, says Richard Fisher of Loyola University Medical School (Chicago, IL), who described the IL-2 clinical trials on behalf of Chiron. Overall, 15 percent of those patients showed a positive response, with 4 percent showing what was deemed a "complete response," says Fisher. The treatment is associated with "severe toxicities," he adds, including an "on-study death rate of 4 percent." Toxicities include nausea, hypotension, renal toxicities, neurological effects, and sepsis. In most cases, however, with proper and close patient management, those adverse effects are reversible.

Though IL-2 is only marginally effective against renal cell carcinoma, no other treatment is effective against the fatal disease.

Questioning IL-2's benefit

Although most members of the advisory committee agreed the drug has a "biological benefit," several committee members voiced doubts about its "clinical benefits." Treatment with IL-2 seems to shrink malignancies in some patients, but committee members questioned whether treatments are worth the risk of death and the other side effects. "I remain unconvinced that it's changed the natural history of disease in these patients," says Ernest Borden of the Medical College of Wisconsin Cancer Center (Milwaukee). "A subpopulation did have biological responses, and that should correlate with clinical benefit, which I'm still not sure was demonstrated," agrees Janice Gabrilove of Memorial Sloan Kettering Cancer Center (New York).

"There are no data that treatment changed the median survival of patients, and many patients go through therapy with no benefit," says Frederick Appelbaum of the Fred Hutchinson Cancer Research Center (Seattle, WA), who served as advisory committee chairman. "But I do feel that a small group of patients stands to gain significantly." Added Jordan Gutterman of the M.D. Anderson Cancer Center at the University of Texas (Houston), "I have a high comfort level that this compound does benefit a fraction of patients. It's obvious IL-2 is toxic, but if we were sitting here 40 years ago, we would have wrestled with the same questions considering conventional chemotherapy."

A $1-million cure

Most of the committee members agreed to recommend to FDA that IL-2 be made available so that physicians and patients could decide whether treatments with it are worth the risk and cost. Treatment and hospital stays for such patients are estimated to cost $30,000 (including $7,000 for the drug) barring serious complications, and $45,000 if the hospital stay entails treatment in an intensive-care unit. "When you factor in patients who don't respond, the cost of IL-2 comes out to nearly $1 million per complete recovery," Appelbaum points out.

Several individuals representing cancer patients who spoke before the advisory committee in favor of IL-2 were less concerned with risks than with potential benefits. For example, Eugene Schonfeld, who is president of the National Kidney Cancer Association (Chicago, IL), pointed to instances where insurance companies have refused to pay for IL-2 treatment of patients because the FDA has not licensed the product. "While there is no legal basis for linking reimbursement to FDA approval," he notes, "every member of this committee understands that if IL-2 had been approved in 1990, these patients would not have been denied reimbursement."

Joanne Freundlich, representing the Cancer Patients Action Alliance (Brooklyn, NY), also implored the committee to act favorably on IL-2. "It's shameful to have life-saving drugs available, and to withhold them," she says. "It goes beyond issues of good science into the realm of ethics. To be blunt, terminally ill people are not worried about long-term side effects. Cancer has bad side effects, too."

—Jeffrey L. Fox