NEXT HURDLE FOR RADIOLABELED ANTIBODIES: ACCEPTANCE BY MEDICAL INSURERS

Biotechnology companies augment clinical trials to address cost effectiveness. Makers of first approved product promise cost-saving detection of colorectal cancer afflicting 150,000 annually in U.S.

THE U.S. FOOD AND DRUG Administration on December 30 announced the first approvals of cancer imaging agents using a monoclonal antibody: OncoScint CR/OV for use in detecting colorectal and ovarian cancer. The FDA's action marks the official beginning of a market expected to mushroom to $250 million in five years. But the success or failure of specific antibody products now more than ever depends on reimbursement decisions as medical insurance and managed care plans, under pressure to control costs, place a growing emphasis on the cost-effectiveness of new technology in addition to safety and efficacy.

"I think we're in pretty good shape for reimbursement," says Jim Geddes, a group vice-president with Cytogen Corp., the Princeton, New Jersey, company that's marketing OncoScint with Knoll Pharmaceutical Co. As many biotechnology companies have begun to do, Cytogen augmented the design of the original clinical trials of its new agent to try to answer questions about cost effectiveness.

Cytogen claims that its data show that OncoScint scans can provide overall savings, even though the procedure is likely to cost patients anywhere from $1000-2000, a price range comparable to computed tomography, which the antibody scan is designed to augment. The list price of OncoScint is $425 per dose. The antibody works in combination with Indiclor, an indium-111 preparation marketed by Medi-Physics, Inc., of Arlington Heights, Illinois at a list price of $450. According to Health Technology Associates, a Washington consulting firm hired by Cytogen to work with third-party payers, Medicare is likely to cover about 80% of the total cost of the radiopharmaceutical and physician services for OncoScint scans.

Cytogen says the antibody scan could guide a surgeon's decision to perform more radical resection, which may improve patient outcome and preclude the risks and costs of follow-up surgery. Or the scan could enable a surgeon to decide that surgery would be futile, preventing the "pain, agony, and extreme expense of surgery that would not have helped the patient anyway," says Mr. Geddes.

Clincal trialists diagnosed patients by conventional means and established a clinical plan, then performed the antibody scan folowed by surgury if indicated. Clinicians then described what they might have done differently based on the information gleaned from the antibody scan. "It's a subjective assessment, but one which begins to answer the outcomes question," says Mr. Geddes. In about 25% of the cases in clinical trials, he says, doctors changed patient management decisions based on the information from the antibody scan.

OncoScint uses the intact monoclonal mouse antibody B72.3 that binds with high specificity to the tumor-associated glycoprotein TAG-72. More than 95% of colorectal adenocarcinomas and a significant portion of other tumors bear the TAG antigen but normal tissues rarely do.

Complementary to CT

The FDA approved the antibody not as a method of initial screening, but for use in presurgical evaluation of patients with recurrent disease in whom scarring and fibrosis might obscure CT or ultrasound. Accordingly, the company is marketing OncoScint as complementary to CT. OncoScint performs poorly in detecting liver metastases due to normal hepatic uptake of ^{111}In. Beyond the liver in the pelvis and abdomen, however, OncoScint imaging may be more sensitive than CT in finding metastases.

The FDA has not approved the repeated use of OncoScint, pending a decision on the risks of immune rejection of mouse antibodies.

At least two other firms have anti-

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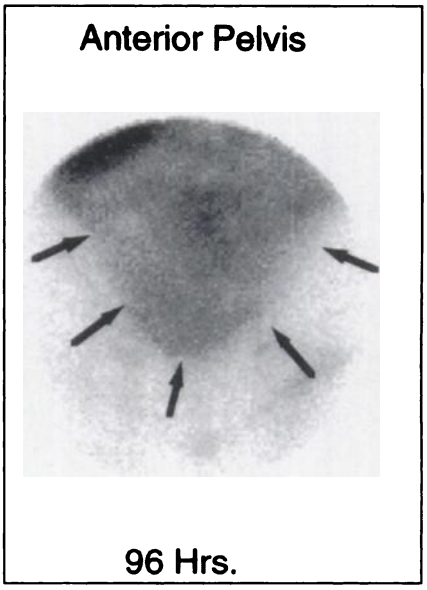

A 63-year-old female, previously treated by surgery and chemotherapy for ovarian carcinoma, complained of abdominal distention and bloating. Computed tomography revealed a small amount of fluid but no definitive findings. The Oncoscint scan shown here revealed widespread disease (dark area) throughout the abdomen. The diagnosis was carcinomatosis, which can not be treated surgically.

Chairman

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Asked about these statements, Dr. Selin said he did not mean to imply any wrongdoing or incompetence on the part of NRC employees. "It's not that the staff was hiding anything from the commission, it's just that information was not drawn together as relevant and brought to our attention," he said, indicating a possible deficiency in the medical program. "On the reactor side it would be unthinkable that a couple of reporters could turn up things staff hadn't," he said.

The chairman dismissed as rumor suggestions that reprisals were in store for certain NRC staff directors. The upcoming transfer of Richard Cunningham, director of the industrial and medical nuclear safety division, had fueled such speculation. Dr. Selin said the transfer was planned prior to the newspaper articles. Dr. Selin said, "We decided quite a while ago that it wouldn't be a bad idea to have someone new take the job." Carl Papperiello, PhD will become director of the division in July.

Whether regulatory changes are forthcoming won't be known until the NRC completes a review of the medical program it began in September, prior to the newspaper series. Dr. Selin said the commission would call an outside panel of medical experts to assess the NRC's internal review.

That panel will not be the Advisory Committee on the Medical Use of Isotopes. Asked why, Dr. Selin said "the reasons are pretty clear" since the ACMUI consists mostly of licensees who practice nuclear medicine and are not sufficiently disinterested in the outcome of regulatory decisions.

One possibility the chairman was able to rule out unequivocally was the NRC taking authority over particle accelerators and x-ray machines. "That's just not our business and its not about to become our business," Dr. Selin said. "We were given authority over the chain reaction and its byproducts. That's always the way it's been and the way it ought to be." ■

OncoScint

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body-based cancer imaging agents nearing FDA approval. Immunomedics Inc. of Morris Plains, New Jersey has filed a complete NDA for ImmuRaid CEA, a labeled fragment of a monoclonal antibody with applications similar to OncoScint. NeoRx Corp. of Seattle plans to complete within months its application for OncoTrac, another labeled antibody fragment, but specific for various forms of lung cancer.

Notably, both firms have eschewed development of intact antibodies, preferring the faster targeting and clearance and limited potential for immune rejection possible with the small molecular subunits of antibodies called fab fragments. With faster targeting, it's possible to radiolabel with the short-lived and widely used isotope technetium-99m.

Since antibody fragments, unlike intact antibodies, clear through the kidneys and could block views of peritoneal cavity in the kidney area, Cytogen decided to stick with a whole antibody labeled with ^{111}In for colorectal and ovarian cancer, says Robert Maguire, MD, a company vice-president. Cytogen concluded from the outset that immunoscintigraphy could not compete with CT scanning for detecting liver disease, so liver uptake of whole antibodies posed no problem.

As investigators began clinical trials with imaging antibodies in the mid-1980s, some analysts predicted that ^{111}In-labeled products would be approved first and that these would be supplanted by ^{99m}Tc-labeled agents, says the president and chief executive officer of NeoRx, Paul Abrams, MD. "We have always believed that technetium is superior and jumped in from the beginning," he says.

Biotechnology firms developing imaging antibodies are leading with products for lung and colorectal cancers since they are the most prevalent forms of the disease. Physicians diagnose about 160,000 new cases of lung cancer in the U.S. each year. Colorectal cancer strikes about 150,000 people annually in the U.S. Early detection of the initial presentation and recurrent disease is crucially important. Ovarian cancer strikes about 21,000 women in the U.S. each year, accounting for 4% of all cancers among women.

Like Cytogen, NeoRx structured its clinical trials to derive data to support third party reimbursement. Dr. Abrams says the trials support the use of OncoTrac as a first-line test for clincal staging of patients suspected of having small-cell lung cancer rather than as an additive test.

"We're in a strong position to get third party payment," he says. "If one has a test where data support that it be done first, invariably it will be reimbursed." The company cites a positive predictive value of 97-98%, which would make the antibody scan as accurate as an entire battery of conventional tests.

Some industry sources say the approval of OncoScint means that "the dam has finally broken" and that the government has paved the way for processing radiolabeled antibody applications. The process stalled briefly due to the overlapping jurisdictions of FDA's center for biologics and the center for drugs. Biologics has assumed the lead for radiolabeled antibodies even though the center for drugs has customarily handled radiopharmaceutical approvals.

The FDA's A. Eric Jones, MD, cautions that the speed of subsequent imaging antibody approvals will still depend mostly on how complete and well-organized the data are for each new agent. "Each company is going to have their own first experience," the group leader for medical imaging says.

Nevertheless, stock values for all three biotechnology companies surged after the FDA's end-of-the-year approval announcement. Market analysts estimate that OncoScint CR sales in the U.S. may reach $22 million in 1993 and $50 million in 1994. Eventual annual sales could reach $240 million. Oncoscint OV sales could reach $4 million in 1993 and $12 million the following year. ■