Monoclonal Antibody Scan Holds Promise for Prostate Cancer Staging

A new radiopharmaceutical under FDA review could help determine patient management for prostate cancer. It may also become a litmus test to gauge the acceptance of monoclonal antibody scans in the field of oncology.

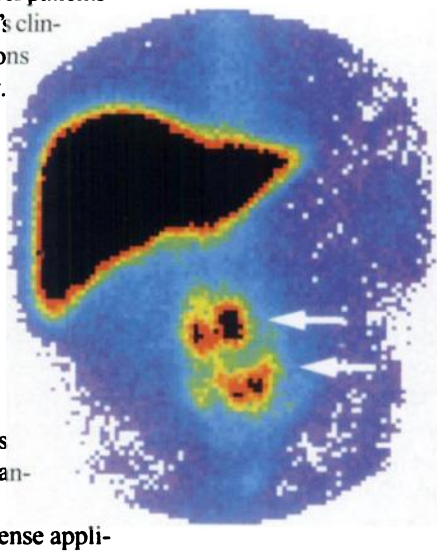
When Washington, D.C. Mayor Marion Barry was diagnosed with prostate cancer last November, the biggest question was whether to treat the cancer and, if so, how aggressively. Consider another dilemma: A man has a rising prostate-specific antigen (PSA) following a prostatectomy but has no signs of recurrence by physical exam or standard tests. Both scenarios are familiar to urologists who must make tough treatment decisions.

A new monoclonal antibody, submitted for approval to the Food and Drug Administration (FDA), may fill in some pieces of the diagnostic puzzle. Barry's team of doctors used the nuclear medicine scan to look for prostate cancer spread in his lymph nodes before deciding whether to perform a prostatectomy. He underwent scintigraphy using the monoclonal antibody, ^{111}In-labeled capromab pendetide (ProstaScint, Cytogen Corp., Princeton, NJ). "We wanted to be absolutely sure that the Mayor had no metastatic disease," said Michael J. Manyak, MD, director of urologic oncology at George Washington University Hospital in Washington, D.C. and one of Barry's doctors. "The scan was absolutely negative, and we were very relieved." Barry went on to have a prostatectomy.

Manyak has conducted clinical trials of ProstaScint and said the scan holds promise for evaluating certain subgroups of prostate cancer patients. What is more, urologists are eager for a reliable test that can detect small tumor metastases in the lymph nodes surrounding the prostate. ProstaScint researchers who spoke with *Newsline* said they were "enthusiastic" "hopeful" and "intrigued" by the new monoclonal antibody scan. Monoclonal antibody researchers who were not involved in the Prostascint clinical trials, however, were more tempered in their opinions and questioned the usefulness of such a test, in view the lack of curative treatment options for metastatic prostate cancer.

Prognostic Value in Certain Patients

More than 700 prostate cancer patients have been included in Cytogen's clinical trials at over 40 institutions throughout the country. ProstaScint works by interacting with a membrane glycoprotein found chiefly on prostatic epithelial cells. "If the antigen is localized outside the prostate, we know we have metastatic disease," said Manyak. Since normal prostate cells weakly express the antigen, ProstaScint cannot be used as a screening test for prostate cancer.

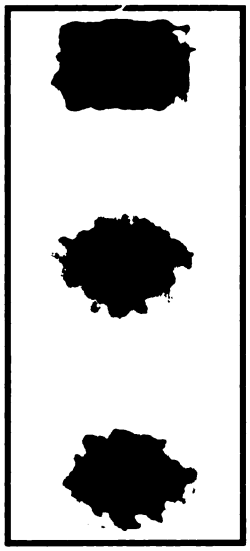


A patient with a positive biopsy for prostate cancer underwent scintigraphy with ProstaScint. The scan shows maked radiopharmaceutical accumulation in the periaortic and left iliac lymph nodes suggestive of metastases to these areas. Bone and CT scans of the pelvis showed no evidence of metastases.

Cytogen filed a product license application with the FDA in January, 1995. "We hope to make a presentation before an FDA advisory panel this year," said Robert Maguire, MD, vice president of medical affairs at Cytogen, the manufacturer of the antibody test.

If approved by the FDA, ProstaScint will be intended for two specific subgroups of patients, according to Maguire. One group is men with newly diagnosed prostate cancer who are deemed to be at high risk for having cancer in their lymph nodes: For instance, they may have a PSA reading of 20 or greater in a proven prostate carcinoma prior to prostatectomy or radiation therapy. Maguire estimates about 10% of newly diagnosed patients could be eligible for this test.

The monoclonal antibody test could also benefit a second group of patients who have an elevated PSA level following a prostatectomy. The scan could help differentiate whether a rise in PSA is due to recurrent/residual disease in the prostate bed or due to metastases in the pelvic or abdominal lymph nodes. It is estimated that 10% to



SPECT image shows ProstaScint accumulation in a biopsy-proven prostate tumor at the left iliac bifurcation and along the left common iliac artery.

30% of patients with a rising PSA have only local recurrence, which means their PSA levels will decline in response to radiation. The other 70% to 90% have metastases to lymph nodes or other distant sites and do not respond to further surgery or radiation.

"After surgery, a rise in the serum PSA tumor marker often can be detected one to three years before clinical evidence of disease shows up on an MRI, CT or bone scan," said Maguire. Since it is extremely difficult to determine who will respond to radiation treatment for residual disease, some patients whose disease exists outside the radiation field are give useless radiation therapy, whereas other patients with local disease are not given radiation.

"The monoclonal test may help identify those patients who can be cured by radiation treatment where we once thought their cancers could only be controlled by hormonal therapy," said Manyak. The key lies in the test's reliability to diagnose which patients have metastases or, more importantly, which patients do not. According to Manyak, the sensitivity rate of a SPECT scan using ProstaScint is 63% and the specificity rate is 72%. "The values are quite good," he said, especially when compared to sensitivity rates of 6% and 15% for CT and MRI.

Prostate cancer researcher Joseph E. Oesterling, MD, a professor and urologist-in-chief at the University of Michigan in Ann Arbor agrees the benefit of the scan lies in its high negative predictive value, which is essential for a prognostic test. "The test clearly has the potential to be part of the staging evaluation in patients with high PSA levels and large tumors," he said.

Encouraging Results from Clinical Trials

Manyak and other researchers involved in the ProstaScint clinical trials have been encouraged by the results. In one study conducted at the University of Texas M.D. Anderson Cancer Center in Houston, researchers performed the scan on 19 patients newly diagnosed with prostate cancer who were surgical candidates despite being at higher risk of having metastatic lymph node disease. Out of the eight patients who had positive lymph nodes, the scan correctly detected metastases in four of them. The test had a negative predictive value of 83% and positive predictive value of 50%. The scan was able to predict disease lesions of 5 mm or greater.

In another study conducted at the University of Iowa College of Medicine in Iowa City, 27 patients, who had undergone radical prostatectomy and were experiencing a rise in PSA, received the ProstaScint scan. The scan detected suspicious lesions in 22 patients, half of which were confirmed by biopsy, CT or MRI. The authors of the study published in *The Journal of Urology* (vol. 152, 1490-1495, November 1994) wrote that the large number of unconfirmed findings do not necessarily mean a high false-positive rate but rather that the needle biopsy for detecting local recurrence is an "imperfect standard" and that CT and MRI are "unreliable."

Despite these favorable results, researchers will need to follow patients who have had the monoclonal antibody scans to ascertain its true predictive value. Michael Haseman, MD, medical director of nuclear medicine at Sutter Community Hospitals in Sacramento, CA, is currently tracking patients to determine if the ProstaScint scan correctly predicted which of them would respond to therapy for localized recurrence.

Potential Pitfalls of the Test

The clinical trial investigators who spoke with *Newsline* said they see few limitations in the ProstaScint test. As with any nuclear medicine scan, Haseman pointed out that the monoclonal scan has

Monoclonal Antibody Radiopharmaceuticals in the FDA Pipeline

OncoScint™ is the only monoclonal antibody so far to have received FDA approval, but a host of new antibody imaging agents are awaiting FDA approval and may become available to nuclear physicians within the next year or two.

✔ **Colorectal Cancer:**: In February, an FDA advisory panel recommended approval for CEA-Scan, a technetium-labeled monoclonal antibody test made by Immunomedics to evaluate patients with colorectal cancer. The FDA panel recommended that the monoclonal scan be used in conjunction with CT to confirm metastases. The panel did not recommend restricting CEA-Scan to a single use. It contains mouse antibody fragments which are less immunogenic than whole mouse antibody, according to David M. Goldenberg, ScD, MD, chairman and founder of Immunomedics. He said the company hopes to have FDA approval by the end of this year. CEA-Scan is also being tested in Phase III clinical trials for lung cancer and in Phase II trials for breast cancer.

Cytogen's OncoScint™, for colorectal cancer, had a recent FDA-approved label change to include multiple imaging in patients with a negative HAMA level.

✔ **Small-Cell Lung Cancer:** Dupont Merck is awaiting FDA approval for Verluma, a technetium-labeled monoclonal antibody for the staging of small-cell lung cancer. The test, which was recommended for approval by an FDA advisory committee, is used to detect distant metastases in both the bones and soft-tissue organs such as the liver. It could replace the need for multiple tests such as bone scans, CT and MRI, according to Robert Williams, director of marketing development at Dupont Merck.

✔ **Prostate Cancer:** Cytogen's ProstaScint is currently under FDA review. The company expects an advisory committee to determine approval status within the next few months. If approved, the antibody imaging agent would be used for two groups of prostate cancer patients: those suspected of having lymph node metastases presurgically and those suspected of having a recurrence postsurgically.

less anatomic resolution than MRI and cannot indicate whether prostate cancer has penetrated the capsule of the prostate gland, which is something surgeons want to know before surgery.

Researchers not involved in ProstaScint trials, however, have more significant concerns. "ProstaScint has several limitations," said Chaitanya R. Divgi, MD, a nuclear physician at Sloan Kettering Memorial Cancer Center in New York who has performed research with monoclonal antibodies. The specificity rate of 72% "is not that high," he said. Patients with false-positive scans may not be given potentially beneficial radiation therapy.

"Another problem is whole mouse antibodies like ProstaScint have been found to be highly immunogenic," said Divgi. The human body recognizes the whole mouse antibody as foreign and makes antibodies—called human antimouse antibody (HAMA)—in response. These HAMA antibodies interfere with absorption of the monoclonal agents. Although ProstaScint works effectively the first time, it may not work as well when used repeatedly, according to Divgi.

Case in point: Cytogen's OncoScint, a monoclonal antibody for colorectal cancer imaging that contains whole mouse antibody, was approved by the FDA for a one-time-only use because 50% of patients had a HAMA response after the initial injection. (The FDA has recently approved a change in the product label allowing the repeated use of OncoScint in those patients who have a negative HAMA level.)

In research protocols for therapeutic monoclonal antibodies, investigators often exclude patients who have received OncoScint scans. "Patients don't want to have a mouse antibody imaging test if it closes off their option for a therapeutic agent further down the road," said Divgi. He said this may have limited the utilization of OncoScint by the medical world.

Taking the one-time-use restrictions into consideration, companies developing therapeutic monoclonal antibodies are using humanized antibodies with only a small fraction of mouse antibody. Since HAMA response is not likely to be a problem, the therapy can be given multiple times. For instance, Immunomedics, a company that develops monoclonal antibodies, is currently testing therapeutic antibody products containing 95% human component and only 5% mouse antibody, according to David M. Goldenberg, ScD, MD, chairman and founder of Immunomedics and president of the Center for Molecular Medicine and Immunology in Newark, NJ.

ProstaScint could receive the same lackluster reception as OncoScint—especially if hospital managers are not convinced of the need for the test given their efforts to trim health care costs. Although Divgi called the results of the clinical trials "encouraging" for presurgical patients, he questions whether ProstaScint will be useful for patients suspected of having a recurrence.

"The monoclonal test may help identify those patients who can be cured by radiation treatment where we once thought their cancers could only be controlled by hormonal therapy."

Oncologists still do not know if the overall survival for those with localized recurrences differs from those with distant metastases. "With medical care becoming more outcome oriented, we need to justify the costs of monoclonal tests to insurance companies and HMOs," Divgi said.

Although economic issues are important and need to be addressed, said Maguire, ProstaScint will be much better received than OncoScint for two reasons: Urologic oncologists feel there is a need for a reliable imaging agent to detect metastatic prostate cancer, which did not seem to be the case for colorectal cancer. Also, ProstaScint has a greater potential for repeated use since only 5% of patients injected with the agent have a HAMA reaction—a much smaller percentage than those injected with OncoScint.

If the radiopharmaceutical is approved by the FDA, only time will tell if ProstaScint imaging will become part of a diagnostic protocol for prostate cancer. Cytogen estimates 60,000 prostate cancer patients could benefit from this test every year. Some could be spared unnecessary radiation or surgery. Others, like Mayor Barry, could be reassured by the test and learn that a potential for a cure is available to them.

—Deborah Kotz

Educational Efforts for ProstaScint Scan

Anticipating FDA approval for ProstaScint, Cytogen is now organizing an educational effort to teach nuclear physicians how to perform and interpret scans using the antibody. The company has sent technical experts to about 35 institutions so far to teach prostate cancer teams that include a urologist, radiation oncologist and nuclear physician. The experts–often researchers who were involved in the clinical trials–review a minimum of 10 cases in which the scan was used.

"These scans are difficult to interpret," said ProstaScint researcher Michael Haseman, MD, medical director of Sutter Community Hospitals in Sacramento, CA. "The typical nuclear medicine physician is not familiar with the lymph node anatomy of the pelvis, so there is a learning curve."

If ProstaScint is approved by the FDA, Cytogen will offer the training program to hospitals throughout the country.