Tempers Flare Over Fate of Prostate Cancer Drug

BY BETSY BATES
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Controversy is a fact of life for pharmaceutical companies and the Food and Drug Administration but the saga of an investigative immunotherapeutic agent for advanced prostate cancer has been unusually contentious.

The struggle to gain FDA approval for sipuleucel-T, to be marketed as Provenge by Dendreon Corp., has included a raucous FDA meeting, picketing in Washington, congressional lobbying, and a lawsuit.

A final decision about whether to approve the drug now awaits interim findings from a 500-patient phase III trial, but in the meantime, the dispute has ignited activism reminiscent of the efforts to get HIV drugs "fast tracked" in the 1980s.

The dispute has raised questions about whether biologic agents can be judged by the same efficacy standards as traditional drugs, particularly when the goal is to treat terminal patients with few alternatives.

It has also generated concern in some scientists about the increasing influence of "antiscience" voices in American life. And finally, it has highlighted media pressure on the scientific community to justify established principles guiding medical policy decisions in the face of tearful families and angry investor campaigns.

It began March 29, when officials of the Seattle-based biotech firm presented to the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee the results of two fast-tracked, phase III parallel studies of their biologic agent in a total of 225 men with asymptomatic, hormone-refractory, metastatic prostate cancer.

Sipuleucel-T would be the first oncologic drug in a new class, designed to stimulate a patient's immune system with a "vaccine" made from his own peripheral blood mononuclear cells, including antigen-presenting cells. The cells would be extracted by plasmapheresis and flown to a centralized laboratory, where they are activated with a recombinant fusion protein containing prostate antigen fused to GM-CSF, an immune cell activator. Within 3 days of collection, the cells are reinfused into the patient in an outpatient procedure.

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Activists demand FDA approval of Provenge during a Sept. 18 protest in front of the agency's offices in Rockville, Md.

After the March meeting, at least two committee members, oncologist Howard I. Scher of Memorial Sloan-Kettering Cancer Center, New York, and Dr. Maha Hussain, professor of internal medicine and urology at the University of Michigan, Ann Arbor, wrote to the FDA to express concern about the implications of approving the drug based on the evidence. The letters were leaked and reprinted, first in The Cancer Letter, then online.

Dr. Scher said inconsistent trial data "do not constitute 'proof' of benefit or justify a conclusion that they are 'reasonably likely' to predict benefit. … The only conclusion is that the survival difference observed may have occurred by chance alone."

The company had argued that the survival results were "clinically meaningful, significantly persuasive, and internally consistent in the intent-to-treat population."

A 4.5-month survival benefit from a drug with few side effects is urgently needed by prostate cancer patients, who now gain only about a 2-month survival advantage from docetaxel (Taxotere), a drug with side effects that many patients find debilitating.

On May 9, the FDA rejected the committee suggestion to approve sipuleucel-T, requesting more data from Dendreon.

The decision sparked a debate about whether the FDA's restraint represented a scientifically valid concern about the efficacy of a treatment that failed to pass muster in clinical trials, or a risk-averse philosophy depriving patients of treatments that offer them their only hope of prolonged survival.

Within the month, Dr. David Penson of the University of Southern California, Los Angeles, presided over a press briefing at the annual meeting of the American Urological Association marked by frustration about the decision. He listed three reasons the FDA might reject a recommendation to approve a drug: safety, efficacy, and politics. "[We] were really hoping this would be approved, because these patients have so few other options," he said.

After the July 30 filing of a federal lawsuit by Care to Live, an Ohio nonprofit organization seeking an emergency injunction that would make the drug available to cancer patients, an FDA spokeswoman said the agency could no longer comment on the issue. A U.S. Court of Appeals, District of Columbia Circuit, in early August ruled that patients do not have a constitutional right to unapproved drugs, in a suit brought by the Abigail Alliance for Better Access to Developmental Drugs. The Alliance has vowed to appeal.

Dendreon announced that the FDA had decided to accept either a positive interim or final analysis of survival from its ongoing, phase III, 500-patient IMPACT study as the basis for amending the Biologics License Application that was filed on a fast-track basis in early 2007, possibly paving the way for approval as soon as 2008. ■

Robotic Prostatectomy Has Relatively Few Complications

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — Robotic radical prostatectomy had a complication rate of about 5.1% and promising medium-term outcomes, according to a large case series presented in two posters at the annual meeting of the Society of Laparoendoscopic Surgeons.

This complication rate is similar to those reported in large series of open radical prostatectomies and lower than those reported in laparoscopic and other robotic series, wrote Dr. Pankaj P. Dangle and colleagues from The Ohio State University Medical Center, Columbus.

According to the first poster, among 1,256 procedures performed by a single surgeon (Dr. Vipul R. Patel), there were 64 complications: 2 intraoperative, 16 perioperative, and 46 postoperative. No patients died, and no patients had to be converted to open repair.

Four patients had myocardial infarctions, four required blood transfusions, and three had pulmonary emboli.

Anastomotic leakage was the most common complication, occurring in 1.75% of the cases.

Other indicators also pointed to a learning curve with robotic radical prostatectomy. For example, the overall complication rate was 9.33% among the first 300 patients, but 3.37% among the last 300 patients.

In the second poster, the investigators extended the case series to 1,500 patients, with all procedures performed by Dr. Patel over a 56-month period. As in the original series, he used the da Vinci Surgical System, and he performed the procedure transperitoneally using a six-trocar technique.

The patients' average age was 61, and their mean body mass index was 29 kg/m^2. Their mean prostate-specific antigen was 8.65 ng/mL, and their mean Gleason score was 7. The operation took an average of 105 minutes, with a range of 55-300 min. On average, patients lost 111 mL of blood, with a range of 50-500 mL.

Overall, 97% of the patients were discharged home on the first postoperative day, and the mean catheter time was 6.3 days. After 3 months, 92% of the patients were completely continent; that number went up to 97% after 6 months and 98% after 12 months.

The investigators, who disclosed that they have no financial relationships related to their presentation, concluded that robotic-assistant laparoscopic radical prostatectomy is a safe, feasible, and minimally invasive alternative for treating clinically localized prostate cancer. ■

Outcomes Worse in Overweight Robotic Prostatectomy Patients

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — Men who are overweight or obese have poorer outcomes following robotic radical prostatectomy, according to a poster presentation by Dr. Jay D. Raman and colleagues at the annual meeting of the Society of Laparoendoscopic Surgeons.

Overweight and obese men had a longer operative time, greater blood loss, and longer hospitalizations, compared with men who had normal body mass index (BMI) values.

The study involved 132 patients with clinically localized prostate cancer. Dr. Raman of New York–Presbyterian Hospital, New York, and his colleagues divided the patients into three cohorts, based on BMI, in which 38 patients had a normal BMI (18-24.9 kg/m^2), 60 were overweight (BMI 25-29.9), and 34 were obese (BMI of 30 or greater).

The groups had no significant preoperative differences in age, prostate-specific antigen level, or biopsy Gleason score. Obese patients had a significantly higher percentage of clinical T1c cancers (84%), compared with overweight (67%) and normal-weight (55%) patients. Obese patients also had a significantly lower percentage of T2 cancers (16%), compared with overweight (31%) and normal-weight (45%) patients.

The surgery took an average of 304 minutes in obese men, significantly longer than the 235 minutes among overweight men and 238 minutes among normal-weight men.

Normal-weight men lost an estimated 234 mL of blood on average, significantly less than the 318 mL among overweight men and 316 mL among obese men.

Men of normal weight also had significantly shorter hospitalizations: 1.1 days on average, compared with 1.6 days for overweight men and 1.7 days for obese men.

There were no significant differences among the groups in bilateral nerve-sparing (90% overall), open conversion (2% overall), and positive margins (17% overall). Nor did the investigators find significant differences in the complication rate, which was 8% among normal-weight men, 5% among overweight men, and 6% among obese men.

Robotic radical prostatectomies are "technically more challenging" in men with elevated BMI, the authors said. ■