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Health Sciences Center in Denver, a lead investigator in the PLCO trial, and Dr. Fritz H. Schroeder, professor and chair of urology at Erasmus University in Rotterdam and principal investigator for ERSPC.

From 1993 to 2001, PLCO randomized 77,000 men aged 55-74 years to either annual screening (PSA testing for 6 years and digital rectal exam for 4 years) or usual care, which sometimes included screening. The PSA cutoff for biopsy was 4 ng/mL.

At 7 years, prostate cancer had been diagnosed in 2,820 in the screening group and 2,322 in the control group, a significant difference. At 10 years, there were still significantly more cancers diagnosed in the screening group (3,452 vs. 2,974).

Follow-up at 7 years also showed that 50 men had died from prostate cancer in the screening group and 44 in the control group, a nonsignificant 13% difference. By year 10, with data in for 67% of the subjects, 92 in the screening group and 82 in the control group had died, also a nonsignificant difference. The difference remained nonsignificant when the data were analyzed by tumor stage or previous screening at baseline.

"The follow-up may not yet be long enough for benefit from the earlier detection of an increased number of prostate cancers in the screening group to emerge," Dr. Gerald Andriole of Washington University, St. Louis, wrote in the published paper. However, "we now know that prostate-cancer screening provided no reduction in death rates at 7 years and that no indication of a benefit appeared with 67% of the subjects having completed 10 years of follow-up."

ERSPC analyzed outcomes in men aged 50-74 years from seven health registries. Patients were randomized to PSA screening once every 4 years or to no regular screening. The screening protocol varied by country; PSA cutoffs triggering more investigation ranged from 2.5 to 4 ng/mL.

Researchers found 5,990 prostate cancers in the screening group vs. 4,307 in the control group. But the increased diagnoses carried a price. Of the men who underwent biopsy for an elevated PSA, 76% had a false-positive result. The positive predictive value of a prostate biopsy was also low—just 24% on average.

'Death from prostate cancer in 7 years is meaningless' because the average interval between prostate cancer recurrence after radical prostatectomy and death has been shown to be 13 years.

In a preselected core group of men aged 55-69 years, there were significantly more prostate cancer deaths in the control group (326 vs. 214; odds ratio 0.80). In the intent-to-screen analysis, which included all subjects, the absolute difference between the screening and control groups was 0.71 deaths/1,000 men, yielding 1,410 screenings and 48 cancers to prevent 1 prostate cancer death.

Criticism of PLCO Study

The PLCO study garnered criticism at the meeting from specialists who said the research was seriously flawed and that public confusion regarding the finding of no mortality reduction with screening could prevent many men from seeking a test that could predict their future risk of prostate cancer and ultimately reduce mortality.

During the press briefing, Dr. William J. Catalona, medical director of the Urological Research Foundation and director of the clinical prostate cancer program at the Robert H. Lurie Comprehensive Cancer Center at Northwestern Memorial Hospital, Chicago, described PLCO as "just a snapshot taken halfway around the track" that has been incorrectly promoted as the "Holy Grail."

"This isn't a trivial matter, because giving the wrong message out to the public could dissuade men from undergoing potentially life-saving testing and potentially life-saving treatment," said Dr. Catalona, who moderated the press briefing, which was also attended by Dr. Crawford and Dr. Schroeder. Dr. Catalona, who developed the PSA test, disclosed that he receives research support from Beckman Coulter Inc., a manufacturer of PSA assays, and from deCODE Genetics of Rejkavik, Iceland.

"Death from prostate cancer in 7 years is meaningless" because the average interval between prostate cancer recurrence after radical prostatectomy and death has been shown to be 13 years, he said. ERSPC also did not see an improvement in survival with screening at 7 years, Dr. Catalona noted. However, the mortality curves for the screening and control arms of the study began to diverge at about 7-8 years and continued to do so over time.

PLCO's use of the PSA cutoff of 4 ng/mL for biopsy and the fact that fewer than half of subjects in the screening arm actually underwent a biopsy also point to serious problems, he said. "How could anybody expect a trial like this to show that screening saves lives when the people who are screened don't get a biopsy? If the PLCO people had set out to design a study that would discredit PSA testing, it would be difficult to do a better job. And if they wanted to simulate what would happen if every man in the United States got tested for PSA but few followed up with a biopsy or treatment, we could have guessed the answer."

Reductions in death rates with PSA screening are appearing in World Health Organization databases in westernized countries where PSA testing is widespread, Dr. Catalona said. "These studies are not a message in the wilderness. They unequivocally demonstrate that PSA testing, if done right, can save lives."

Dr. Carroll said in an interview that contamination in the PLCO study diluted its ability to show a difference between the two study groups.

Approximately 40% of men in the study had undergone PSA testing in the previous year. "That culls out cancer that may have been detected during the trial," he said. Further, at least 53% of men in the control group actually received PSA screening. "We think that number may actually be much higher, because virtually all of the cancers detected [in this group] were stage 1 and 2, which are virtually always detected by PSA and DRE."

To recommend a biopsy, the study used a single PSA cut point rather than PSA in conjunction with family history, ethnicity, and other factors that may play a role in prostate cancer risk. "Based on the PLCO trial, you cannot say that early detection does not reduce mortality. The European trial showed that it did," he said. ■

Michele G. Sullivan contributed to this report.

Provenge Shows Survival Benefit in Prostate Cancer

BY SUSAN BIRK

CHICAGO — Autologous active cellular immunotherapy with sipuleucel-T, the controversial investigative agent with the brand name Provenge, extended survival by a median of 4.1 months in men with metastatic androgen-independent prostate cancer, according to the most recent data from the IMPACT study.

The much-anticipated results of the phase III, multicenter, randomized, double-blind, placebo-controlled trial were presented in a late-breaking science forum at the annual meeting of the American Urological Association.

"The data show that sipuleucel-T is the first active immunotherapy to demonstrate an improvement in overall survival for advanced prostate cancer," said coinvestigator Dr. David F. Penson of the University of Southern California in Los Angeles.

"Provenge appears to have a highly favorable benefit-to-risk profile [and] a short duration of therapy, and perhaps most importantly, will not only change the way we manage prostate cancer, but also has the potential to create an entirely novel therapeutic paradigm across the field of oncology," he said.

Median survival reached 25.8 months with treatment and 21.7 months with placebo. The 3-year survival rate was 31.7% with treatment and 23% with placebo, a relative increase of 38% ($P = .032$). The hazard ratio was 0.775, indicating a 22.5% reduction in the risk of death in the sipuleucel-T treatment arm.

The experimental vaccine from Dendreon Corp. still had not met the primary end point when interim results from the IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial were made public in fall 2008. An earlier Food and Drug Administration decision not to approve Provenge, pending more data, had triggered demonstrations by patient advocates of the therapy.

The IMPACT trial included 512 patients with minimally symptomatic or asymptomatic advanced androgen-independent prostatic adenocarcinoma with metastasis to lymph nodes or bone, who had a life expectancy of at least 6 months and a serum prostate-specific antigen (PSA) level greater than 5 ng/mL. They were randomized at a 2:1 ratio to receive the experimental vaccine or a placebo. In all, 90% of patients completed treatment.

The active cellular immunotherapy is designed to stimulate and optimize production of the patient's T cells and to enlist these cells in the destruction of specific tumor cell types.

At the time of disease progression, patients in both arms of the study were able to receive treatment at the physician's discretion. Patients who were randomized to placebo had the option of receiving immunotherapy in which they received a version of sipuleucel-T prepared from their own cryopreserved cells, which had been harvested at the time of placebo generation. Patients randomized to sipuleucel-T had the option of receiving an additional dose of docetaxel (Taxotere).

The investigational therapy produced only minor—in most cases, transitory—side effects, Dr. Penson said.

This favorable safety profile makes the immunotherapy particularly promising as a treatment for patients with terminal prostate cancer because it preserves quality of life while prolonging life, he said.

The survival benefit found with sipuleucel-T in this study has major significance for patients with advanced prostate cancer, he said. "When you consider that these patients have less than a 2-year survival advantage on average, and you're going to give them 4 more months of life, that's a 20% advantage."

To rule out the possibility of the survival benefit being driven by a particular group of patients, the treatment effect was assessed in multiple population subsets. All subpopulations demonstrated a positive treatment effect, Dr. Penson reported.

The survival benefit of sipuleucel-T shown in this study is consistent with two earlier multicenter, randomized, double-blind, placebo-controlled trials of the agent, Dr. Penson said. An integrated analysis of the three studies, which includes a total of 737 patients, reveals a hazard ratio of 0.735, which represents a 26.5% reduction in the risk of death, with a P value of less than .001, he said.

Dr. Penson said that he had no disclosures related to the study. ■