Clodronate May Slow Bone Metastasis in Prostate Cancer

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SAN FRANCISCO—Oral sodium clodronate appears to have delayed progression of bone metastasis from prostate cancer in a randomized clinical trial, although the results did not reach statistical significance. British investigator David Dearnaley, MD, presented the preliminary results on behalf of the Medical Research Council (MRC) Clinical Trials Unit at the 37th Annual Meeting of the American Society for Clinical Oncology (ASCO) in San Francisco.

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Despite longer time to progression and better survival for those patients who received clodronate, Dr. Dearnaley said the gains were not strong enough to support the growing use of bisphosphonates in prostate cancer patients. Instead, he urged that the findings be used to design new trials with more powerful agents (see related article).

"We believe these results are interesting and intriguing, but inconclusive, and should be a motivation for further larger trials to confirm or reject these findings, perhaps using more potent third-generation bisphosphonates and an IV route of administration," said Dr. Dearnaley, the Bob Champion Senior Lecturer, Royal Marsden NHS Trust and Institute of Cancer Research, Sutton, England.

The investigation focused on clodronate because bisphosphonates have been shown to slow bone metastasis in breast cancer and myeloma, and to diminish bone pain in prostate cancer patients.

From 1994 to 1998, the trial enrolled 311 patients from 33 centers, including one in New Zealand. All had proven bone metastasis on a bone scan and were either starting or responding to initial hormonal therapy. Median follow-up was 43.5 months.

The trial was divided into two arms. A group of 159 patients received 2,080 mg of oral sodium clodronate in four tablets daily for 3 years or until reaching one of the primary endpoints of the study: symptomatic bone progression or death. A balanced cohort of 156 men received four placebo pills daily with the same guidelines.

Study Results

As of early April, 220 of the 311 participants had reached a primary study endpoint. The main reason for stopping treatment was symptomatic bone progression, which occurred in 186 patients: 52% of the placebo arm and 43% of the clodronate arm. Actuarial curves show a difference of 4.3 months in the median time to progression: 19.3 months for the placebo arm vs 23.6 months for the clodronate arm.

Survival outcomes were also better for the patients on clodronate. Their median survival was 36.8 months, compared with 28.4 months for the placebo group. At 2 years, 69% of the clodronate group was still alive vs 63% of the placebo group. Although 103 patients died in the control group compared with 10 more in the clodronate group, Dr. Dearnaley said the causes of death were similar.

He noted that 15% of patients stayed on the trial medication for 3 years. At 2 years, 49% of the clodronate group was event free, compared with 41% of the control group.

Despite the data favoring the clodronate arm, Dr. Dearnaley warned against a definitive interpretation of the results. "We've shown an estimated 2-year reduction in symptomatic bone
progression of prostate cancer of 8.5%. The trial was designed to detect an 11% difference at 2 years, so our result is not statistically significant," he said.

**Adverse Events**

Gastrointestinal problems caused 9% of patients in the clodronate group, but only 1% of patients in the placebo arm, to leave the trial. About one third of patients in the clodronate group had their dose modified, usually reduced rather than stopped.

Other adverse events were described as asymptomatic. These included raised LDH levels and hypocalcemia in five patients. "I have to say none of these side effects was what I would call serious," Dr. Dearnaley said.

**Other Findings**

One potentially important observation was that the time from when a patient was diagnosed to when he entered the trial seemed to matter. Patients who started taking clodronate earlier in their treatment had better results.

"It may be that we were already beginning to see patients failing at the time we started the bisphosphonate," Dr. Dearnaley said. "There is a strong indication that we ought to come in with bisphosphonates on day 1 of hormone treatment, if we want to push this hypothesis as far as it can go. I think this is important for any further trials."

Another provocative finding was a relative reduction of prostate-specific antigen (PSA) in the clodronate group. A 20-month analysis of the data showed a median PSA level of 3.7 ng/mL in the clodronate group vs 6.8 ng/mL in the placebo arm. "There’s a suggestion of biological activity based on the follow-up PSA level," he said, "and a suggestion of greater activity if patients are started on the drug when newly diagnosed."

In response to a question, he agreed that, based on his data, there is no reason to use bisphosphonates outside of a clinical trial in patients with prostate cancer. "I think that’s very fair," he said. "... [even for pain] the data for using bisphosphonates in prostate cancer are very weak."

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