

Study: CA 125 Best Sole Biomarker for Ovarian Ca

BY DOUG BRUNK

No screening biomarker appears to work better than CA 125 alone in detecting ovarian cancer, according to an analysis of prediagnostic specimens from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

During a teleconference from the annual meeting of the American Association for Cancer Research, Dr. Daniel W. Cramer reported on a collaboration between the National Cancer Institute's Early Detection Research Network (EDRN) and the Specialized Programs of Research Excellence (SPORE) to compare the best screening markers for ovarian cancer, first in case-control specimens that were drawn at the time of diagnosis (phase II specimens from 160 cases), then in blood that was drawn months or years prior to diagnosis (phase III specimens from 119 cases) among women enrolled in the PLCO (Prostate, Lung, Colorectal,

and Ovarian Cancer) screening trial.

Funded by the NCI, the PLCO trial enrolled more than 150,000 men and women aged 55-74 years to be studied by various screening arms, including one to test CA 125 (cancer antigen 125) and pelvic ultrasound for ovarian cancer, between 1992 and 2001.

"The first question we wished to answer was how much we can infer about a test's performance in prediagnostic specimens based upon their performance at the time of diagnosis," said Dr. Cramer, professor of obstetrics and gynecology at the Brigham and Women's Hospital and Harvard Medical School, both in Boston. "The second question we wished to answer was whether a panel of markers can add value over a single marker alone, with the current standard being CA 125."

More than 24 different markers and 4 panels of markers were studied. Dr. Cramer reported that the top-performing marker was CA 125, followed by human epididymis protein 4 (HE4) and CA 72-4.

"Moving from the phase II specimens to the phase III specimens, there was a predictable loss in the performance soonest for markers that might be identified as acute phase reactants," he said. "But we also found that even the standard markers like CA 125 seemed to lose their value as you got more remote from diagnosis."

At best, marker panels and algorithms tested in the study added "marginal improvement" over CA 125 alone.

Although the PLCO concluded that general population screening with combined CA 125 and transvaginal ultrasound cannot be recommended, a larger trial in the United Kingdom recently concluded that screening was "feasible" (Lancet Oncol. 2009;10:327-40). In that trial, measurement of CA 125 followed by transvaginal ultrasound as a second-line test was able to achieve a sensitivity of 89.5%, a specificity of 99.8%, a positive predictive value of 35%, and a ratio of surgeries to detected cases of 2.3.

"The differences between the two tri-

als were due to the use of CA 125 before referral for ultrasound and improvement in sensitivity and specificity with serial CA 125 testing," Dr. Cramer explained.

Although general population screening for ovarian cancer cannot be recommended now, he said, "I think the foundations for moving it forward can be clearer." This can be accomplished, he proposed, by conducting blood tests followed by ultrasound for positives, not imaging as a primary modality; by using serial CA 125 rather than a static cutoff, and by investigating whether serial markers or the addition of epidemiologic variables can further improve performance.

"I think the NCI should form a stakeholder panel to explore the feasibility of starting a screening trial of ovarian cancer, or at least a demonstration project," he concluded.

The study was sponsored by the NCI's EDRN and SPORE. Dr. Cramer reported that he had no conflicts to disclose. ■

Bisphosphonate Holiday: Pros, Cons

BY SHERRY BOSCHERT

SAN FRANCISCO — How long to continue bisphosphonate therapy after the first few years is an open question, with some validity to each of the possible answers, according to Dr. Steven T. Harris.

"This is a hot-button issue. It comes up all the time," he said at a meeting on diabetes and endocrinology sponsored by the University of California, San Francisco. There are limited data to guide clinicians on how long to extend bisphosphonate therapy, and whether it's risky for patients to interrupt treatment with a drug holiday.

"From my perspective, there is no clinical mandate that says after x number of safe years of therapy, you have to stop," said Dr. Harris of the university. For some patients who have been on daily bisphosphonates for years and who are tired of coordinating their lives around taking the drug on an empty stomach with plain water, a drug holiday lasting a few years probably is acceptable, the data suggest.

Concerns about continuing bisphosphonates for decades revolve around the misconception that the drug "must be building bad bone or brittle bone or crummy bone—abnormal bone. That's absolutely not true," said Dr. Harris, who has been a consultant for and received event funding from companies that make bisphosphonates. Bone biopsies done after 5 years of risedronate therapy or 10 years of alendronate therapy have shown histologically normal bone. More importantly, fracture rates remained lower than with placebo therapy after 7 years of risedronate therapy or 10 years of alendronate therapy, studies have shown. If bisphosphonates built abnormal bone, "you'd expect to see the fracture rates go up with extended therapy," Dr. Harris explained.

For high-risk patients (however one defines that), it's reasonable to continue bisphosphonate therapy, he said. For example, for a 72-year-old patient with a T score of -3.4 who broke her wrist 3 years ago and has three compression fractures, "are you really going to stop her bisphosphonate after 5 years? I think not."



On the issue of interrupting bisphosphonate therapy with a drug holiday, the key data come from the FLEX (Fracture Intervention Trial Long-Term Extension) study of 1,099 postmenopausal women who had taken alendronate for 3-6 years and were randomized to 5 more years of therapy (5 or 10 mg daily) or placebo (JAMA 2006;296:2927-38).

Those who continued alendronate had a significantly lower risk of having a clinical vertebral spine fracture, defined as a painful fracture causing someone to seek medical attention (relative risk, 0.45 compared with placebo). There were no significant differences between the groups in rates of morphometric spine fracture or nonspine fracture.

The gains in femoral neck and total hip densities that were seen in all patients during the first 3 years of bisphosphonate therapy remained stable in those who continued with the drug; however, the densities drifted down in those who were on placebo, so that there was a small but statistically significant difference between the groups 5 years after randomization.

Moreover, the difference between the groups in the number of clinical vertebral fractures amounted to an absolute relative risk reduction of 2.9%—from 5.3% in the placebo group to 2.4% in the alendronate group—for a relative risk reduction of 55%.

An unpublished subgroup analysis of the FLEX study data by other investigators showed that stopping or continuing alendronate made no difference in the risk for nonvertebral fractures in osteopenic patients (defined as those with a T score between -1 and -2.5) but that it did affect osteoporotic patients (those with a T score of -2.5 or lower at randomization). Osteoporotic patients were half as likely to develop nonvertebral fractures (absolute risk reduction, 13%) if they remained on the bisphosphonate, he said.

"If you have a low-risk patient who's been on therapy for years, I do think you can get away with stopping for awhile," Dr. Harris said. Just don't expect the benefits to persist forever, he added, "though it's an issue that is admittedly a bit unsettled." ■

Teriparatide Patch Builds Hip BMD

BY MICHELE G. SULLIVAN

WASHINGTON — A rapid-delivery transdermal teriparatide patch is more effective at increasing total hip bone mineral density than is a daily subcutaneous teriparatide injection, based on the results of a phase II study.

Furthermore, the patch is just as effective as the injection at building lumbar spine bone mineral density (BMD), Dr. Felicia Cosman said at an international symposium sponsored by the National Osteoporosis Foundation.

The phase II trial, sponsored by Zosano Pharma Inc., found that the 40-mcg patch increased total hip BMD by 1.3% in 24 weeks, whereas the daily injected dose failed to increase total hip BMD at all.

The patches are loaded into a cylindrical delivery system. The patient places the patch by pressing the open end of the device against the skin. Once it has adhered to the skin, the quarter-sized patch rapidly delivers the drug, which reaches its peak plasma concentration within just a few minutes. Delivered this way, 40% of the drug is bioavailable.

The placebo-controlled, multidose trial included 165 postmenopausal women (mean age, 64 years). They were randomized to the daily injection (20 mcg), to a placebo patch, or to an active patch of 20, 30, or 40 mcg teriparatide.

After 24 weeks of treatment, all the active comparators resulted in significant BMD gains at the lumbar spine, relative to placebo. Patients using the 40-mcg patch gained a mean of 5% at the lumbar spine. Patients using the 30-mcg patch and taking the daily injections gained a mean of 3.5%, whereas those using the 20-mcg patch gained a mean of 2%. Patients using a placebo patch lost a mean of 0.5% BMD from baseline, reported Dr. Cosman, medical director of the clinical research center at Helen Hayes Hospital in West Haverstraw, N.Y.

Patients using the 40-mcg patch also showed a significant 1.3% increase in total hip BMD. Those using the 30-mcg patch gained 0.5% at the total hip. Patients using the 20-mcg patch, and those using the injectable drug, showed no significant gain in total hip BMD. The placebo patients experienced a BMD decrease of 0.6%.

Adverse events were localized and transient, and included mild to moderate erythema at the patch site.

Dr. Cosman is a paid consultant to Zosano. ■