GYNECOLOGY

WHI: New Findings on Big-Three Cancer Rates

BY BRUCE JANCIN

FROM THE SAN ANTONIO BREAST CANCER SYMPOSIUM

SAN ANTONIO - Menopausal hormone therapy with estrogen plus progestin doubles a woman's risk of death from breast cancer, nearly doubles the risk of death from non-small cell lung cancer, and increases the risk of death from colorectal cancer by 54%, according to an updated analysis of the Women's Health Initiative randomized trials.

Because breast and lung cancer are the top two causes of cancer mortality in women, these are sobering findings with important clinical implications, observed Dr. Rowan T. Chlebowski, professor of medicine at the University of California, Los Angeles.

The 54% increased risk of death after diagnosis of colorectal cancer in Women's Health Initiative (WHI) participants who were randomized to combined-hormone therapy rather than placebo was a trend that didn't achieve statistical significance. But it's nonetheless a finding that crushes the enthusiasm that greeted an earlier WHI report of a 44% reduction in the incidence of colorectal cancer in combined-hormone therapy users after 5.6 years of follow-up (N. Engl. J. Med. 2004;350:991-1004).

Given the initial observation of fewer col-

orectal cancers being diagnosed in the combined-therapy arm of the WHI, investigators were quite surprised by the tumor characteristics of these cancers at time of diagnosis: The colorectal cancers arising in the combined-therapy group – although fewer in number - were much higher risk. In all, 76% of them were pathologically staged as regional or metastatic disease, compared with 48% of colorectal cancers in women on placebo, and 59% percent of the colorectal cancers detected in combined-hormone therapy users were lymph node positive, compared with just 29% in placebo-treated controls.

The WHI consisted of two separate National Institutes of Health-funded, randomized trials that profoundly altered the management of menopausal symptoms. In the early 1990s, more than 40% of all postmenopausal women were on hormonal therapy with estrogen alone or in combination with progestin. Following the initial WHI report of multiple adverse effects of estrogen plus progestin, the popularity of hormone therapy dropped off the table.

One WHI study involved 16,608 postmenopausal women aged 50-79 years with an intact uterus who were randomized to estrogen plus progestin or to placebo for a median of 5.6 years. The other study in-



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DR. CHLEBOWSKI

cluded 10,739 postmenopausal women with prior hysterectomy who were randomized to conjugated equine estrogens alone or placebo for an average of 7.1 years.

In the examination of WHI trends for the big-three (breast, lung, and colorectal) cancers in women, there is a consistent disparity between their relatively modestly increased incidence in dual-hormone therapy users, relative to placebo, and the far larger death rates resulting from these cancers. For example, after 11 years of follow-up, the incidence of breast cancer is up by 25% in the dual-hormone therapy group, relative to placebo. Yet the relative increase in mortality is 96%. Similarly, the incidence of non-small cell lung cancer (NSCLC) was 23% greater in women on combined-hormone therapy than in those on placebo, but the risk of death from NSCLC was 87% greater.

"The greater effect of estrogen and progestin on deaths from breast, lung, and colorectal cancer – [compared with] the effect on incidence - [suggests that] combined-hormone therapy facilitates growth and metastatic spread of established cancers, perhaps mediated by angiogenesis stimulation," the oncologist said, adding that "in a variety of preclinical models, estrogen and progestin are potent angiogenesis stimulators."

Continued on following page

WARNINGS AND PRECAUTIONS: Hypocalcemia and Mineral Metabolism. Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia. In patients predisposed to hypocalcemia and disturbances of mineral metabolism (e.g., history of hypoparathyroidism, thyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis], clinical monitoring of calcium and mineral levels [phosphorus and magnesium] is highly recommended. Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis. Instruct all patients with severe renal impairment, including those receiving dialysis, about the symptoms of hypocalcemia and the importance of maintaining calcium levels with adequate calcium and vitamin D supplementation. Adequately supplement all patients with calcium and vitamin D [see Dosage and Administration, Contraindications, Adverse Reactions, and Patient Counseling Information [17.1] in Full Prescribing Information.

Serious Infections. In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia group than in the placebo group [see Adverse Reactions]. Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with Prolia. Endocarditis was also reported more frequently in Prolia-treated subjects. The incidence of opportunistic infections was balanced between placebo and Prolia groups, and the overall incidence of infections was similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis. Patients on concomitant Immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. Consider the benefit-risk profile in such patients before treating with Prolia. In patients who develop serious infections while on Prolia, prescribers should assess the need for continued Prolia therapy. Serious Infections. In a clinical trial of over 7800 women with p

Dermatologic Adverse Reactions. In a large clinical trial of over 7800 women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate in the Prolia group compared to the placebo group. Most of these events were not specific to the injection site Isee Adverse Reactions). Consider discontinuing Prolia if severe symptoms develop.

Steonecrosis of the Jaw. Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing. ONJ has been reported in patients receiving denosumab *Isee Adverse Reactionsl.* A routine oral exam should be performed by the prescriber prior to initiation of Prolia in treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with Prolia in patients with risk factors for ONJ such as invasive dential procedures, concomitant therapise (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbiid disorders (e.g., periodontal and/or lifting dentures). Good oral hygiene practices should be maintained during treatment with Prolia. For patients who are suspected of having or who develop ONJ while on Prolia should receive care by a dentist or an oral surgeon). In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia therapy should be considered beard on individual benefit-risk assessment. Patients who are suspected of having or who develop ONJ while on Prolia should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia therapy should be considered beard on individual benefit-risk assessment. Patients who are suspected of having or who develop ONJ while on Prolia should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia therapy should be considered based on individual benefit-risk assessment. Patients who are suspected of having or who develop ONJ while on Prolia should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia therapy should be considered based on individual benefit-risk assessment. Patients who ar

- Dermatologic Adverse Reactions [see Warnings and Precautions]

Table 1. Adverse Reactions Occurring in \geq 2% of Patients with Osteoporosis and More Frequently than in Placebo-treated Patients		
SYSTEM ORGAN CLASS Preferred Term	Prolia (N = 3886) n (%)	Placebo (N = 3876) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	129 (3.3)	107 (2.8)
CARDIAC DISORDERS	101 (2.6)	87 (2.2)
Angina pectoris Atrial fibrillation	79 (2.0)	77 (2.0)
EAR AND LABYRINTH DISORDERS	105 (5.0)	107 (/ 0)
Vertigo GASTROINTESTINAL DISORDERS	195 (5.0)	187 (4.8)
Abdominal pain upper	129 (3.3)	111 (2.9)
Flatulence Gastroesophageal reflux disease	84 (2.2) 80 (2.1)	53 (1.4) 66 (1.7)
GENERAL DISORDERS AND	00 (2.1)	00 (1.7)
ADMINISTRATION SITE CONDITIONS	189 [4.9]	155 (4.0)
Edema peripheral Asthenia	90 (2.3)	73 (1.9)
INFECTIONS AND INFESTATIONS		()
Cystitis Upper respiratory tract infection	228 (5.9) 190 (4.9)	225 (5.8) 167 (4.3)
Pneumonia	152 (3.9) 91 (2.3)	150 (3.9) 78 (2.0)
Pharyngitis Herpes zoster	79 (2.0)	72 (1.9)
METABOLISM AND		
NUTRITION DISORDERS Hypercholesterolemia	280 (7.2)	236 [6.1]
MUSCULOSKELETAL AND		
CONNECTIVE TISSUE DISORDERS Back pain	1347 [34.7]	1340 (34.6)
Pain in extremity	453 (11.7)	430 (11.1)
Musculoskeletal pain Bone pain	297 (7.6) 142 (3.7)	291 (7.5) 117 (3.0)
Myalgia	114 [2.9]	94 [2.4]
Spinal osteoarthritis	82 (2.1)	64 (1.7)
NERVOUS SYSTEM DISORDERS Sciatica	178 [4.6]	149 (3.8)
PSYCHIATRIC DISORDERS	170 (4.0)	147 (0.0)
Insomnia	126 (3.2)	122 (3.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		

Suppression of Bone Turnover. In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone furnover and bone histomorphometry [see Clinical Pharmacology [12.2] and Clinical Studies [14.1] in Full Prescribing Information]. The significance of these findings and the effect of hope the degree of suppression of bone remodeling observed with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

ADVERSE REACTIONS: The following serious adverse reactions are discussed below and also elsewhere in the labeling:

- Hypocalcemia [see Warnings and Precautions]

- Dermatologic Adverse Reactions [see Warnings and Precautions]

- Summary of Bone Turnover. In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with science of infections. In the clinical study of 7808 postmenopausal unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fracture, and delayed fracture healing. Monitor patients for these consequences.

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Brief Summary: Consult package insert for complete Prescribing information.

NDICATIONS AND USAGE:
Treatment of Postmenopausal Women with Osteoporosis at High Risk For Facture. Profile is finited or are intolerant to other available osteoporosis from the service of osteoporolic fracture, or multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis multinational study of 7808 postmenopausal women with osteoporosis, Prolia reduces the nicidence of verberta, nonvertienal, and high fractures fee Clinical Studies (I.d.) after several incidence of new malignancies was 4.3% in postmenopausal women with osteoporosis. Prolia reduces the nicidence of verberta, nonvertienal, and high fractures fee Clinical Studies (I.d.) after several incidence of new malignancies was 4.3% in postmenopausal women with osteoporosis. Prolia reduces the nicidence of verberta, nonvertienal, and high fractures fee Clinical Studies (I.d.) after several (I.d.) and patients should response to 1914 prescribing information.

DOSAGE AND ADMINISTRATION: Recommended Dosage, Prolia should be administered by a healthcare professional. The recommended dose of Prolia is of 0mg administered as a single subclusteneous injection in the upper arm, the u

USE IN SPECIFIC POPULATIONS:

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Pregnancy. Pregnancy Category C. There are no adequate and well-controlled studies of Prolia in pregnant women. In genetically engineered mice in which RANK ligand [RANKL] was turned off by gene removal [a "knockout mouse"]. absence of RANKL [the target of denosumab] caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice also showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum (see Use in Nursing Mothers!. Prolia is approved only for use in postmenopausal women. Prolia should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who become pregnant during Prolia treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN [1-800-772-6436] to enroll. In an embryofetal developmental study, cynomolgus monkeys received subcutaneous denosumab weekly during organogenesis at doses up to 13-fold higher than the recommended human dose of 60 mg administered once every 6 months based on body weight [mg/kg]. No evidence of maternal toxicity or fetal harm was observed. However, this study only assessed fetal toxicity during a period equivalent to the first trimester and fetal lymph nodes were not examined. Monoclonal antibodies are transported across the placental in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. Potential adverse developmental effects resulting from exposures during the second and third trimesters have not been assessed in animals (see Nonclinical Toxicology [13.2] in Full Prescribing Information).

Nursing Mothers. It is not known whether Prolia is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Prolia, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Maternal exposure to Prolia during pregnancy may impair mammary gland development and lactation based on animal studies in pregnant mice lacking the RANK/RANKL signaling pathway that have shown altered maturation of the maternal mammary gland, leading to impaired lactation postpartum (see Nonclinical Toxicology [13.2] in Full Prescribing Information).

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Major Finding: After 11 years of follow-up, the incidence of breast cancer is up by 25% in the dual-hormone therapy group relative to placebo. Yet the relative increase in mortality is 96%.

Data Source: An updated analysis of the Women's Health Initiative randomized trials.

Disclosures: Dr. Chlebowski disclosed that he receives grant support from Amgen and is on the speakers bureaus for AstraZeneca and Novartis. Dr. Coates reported having no relevant financial disclosures.

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The investigators' initial hypothesis was that nearly all the increase in breast cancers associated with combined-hormone therapy would involve estrogen receptor–positive tumors. Not so. In fact, the new analysis – based upon 11 years of follow-up and 678 cases of breast cancer – shows that all breast cancer subtypes appear to be increased, relative to rates in the placebo arm.

For example, combined-hormone therapy was indeed associated with an adjusted 27% greater increase in estrogen receptor–positive breast cancers than with placebo in a multivariate analysis, but it was also associated with a 40% increase in estrogen receptor–negative tumors, compared with controls. Also noteworthy were the combined-therapy group's adjusted 78% increase in triple-negative cancers, the twofold increase in HER2-over-expressing tumors, and the 37% increase in HER2-negative tumors.

Nearly all the increase in lung cancer deaths associated with dual-hormone therapy resulted from NSCLC. Hormone therapy had no effect upon small cell lung cancer rates.

Among current smokers, the cumulative risk of death from lung cancer was 3.42% in those who used dual-hormone therapy for 5-plus years and 2.39% in placebo-treated controls. In other words, 1 in 100 current smokers who used estrogen plus progestin for 5-plus years experienced an otherwise-avoidable death from NSCLC. Among past smokers, the rate was 1 in 200. These numbers are worth keeping in mind, given that today roughly 15% of U.S. women are current smokers, and 35% are past smokers, he noted.

Turning to the results of the estrogenalone WHI trial, he pointed out that the therapy had no impact on incidence or death rates from lung or colorectal cancer, relative to placebo, but there was a nonsignificant 20% reduction in the relative risk of breast cancer in the hormone therapy group. This trend for a breast cancer-reduction benefit achieved significance in the nearly 4,500 study participants who were randomized to estrogen alone or placebo 5 years or more following the last menstrual period, where the hormonal therapy group enjoyed a 37% relative risk reduction. Of course, that's not how hormone therapy is ordinarily employed in clinical practice, the physician pointed out.

One audience member rose to say that the oft-quoted sharply increased risk of uterine cancer in women with an intact uterus on estrogen alone dates back to older studies using doses that were considerably higher than those available in contemporary practice, as well as older methods of patient monitoring. What about the possibility of exploring ways to provide estrogen alone to menopausal women with an intact uterus without exposing them to increased uterine cancer risk? she asked.

Dr. Chlebowski said he thinks it's

certainly an appropriate research project, but he'd advise against trying it in clinical practice, given the product labeling and the malpractice lawsuit climate.

His take-home message from the expanded WHI analysis: "Even short-term use of combined-hormone therapy should be reserved for women with limiting climacteric symptoms [that are] not manageable by other means."

In a conference-closing review of the past year's top developments in early breast cancer, Dr. Alan Coates singled out Dr. Chlebowski's presentation on the WHI results as hands-down the most

important study of the year in the field of cancer epidemiology. "As we've known before, there's a small but real increase in the incidence of breast cancer with combined-hormone replacement. The new finding is that there's a massive increase – nearly a doubling – in mortality from breast cancer. And the mortality increase isn't confined to breast cancer. ... This disparate increase in mortality over incidence in several tumor types suggests that the estrogen and progestin [combination] is doing something to the behavior of existing tumors," said Dr. Coates of the University of Sydney.

