5 Minute JournalClub

Effect of High-Dose Vitamin D Therapy on Bone Mineral Density and Anastrozole-Induced Musculoskeletal Pain

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year where published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVE

- Assess the potential effects of high-dose vitamin D therapy on bone mineral density and anastrozole-induced musculoskeletal pain in patients with breast cancer.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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IN THIS ISSUE:

- **Obesity** associated with increased risk of breast cancer recurrence and death
- **Bisphosphonates** associated with lower risk of developing primary breast cancer
- **Vitamin D** replacement for AI-induced musculoskeletal pain and bone loss

A lot of people remember the historic 2005 ASCO Annual Meeting in steamy Orlando for the last-minute "Breast Cancer Education Session" chaired by George Sledge, featuring the first reports of adjuvant trastuzumab in three major Phase III trials, and the initial positive study of bevacizumab in metastatic disease. However, during that same meeting Rowan Chlebowski reported, with decidedly less fanfare, the initial and some might say stunning results of a randomized trial — the WINS study — demonstrating that "adjuvant" dietary counseling to reduce fat intake significantly lowered the risk of breast cancer recurrence. Five years later, we have two huge ongoing second-generation adjuvant trials in HER2-positive disease and a slew of studies evaluating bev in a number of settings, but the impact of diet and exercise on breast cancer progression has been pretty much ignored despite very similar compelling data in colon cancer.

It is interesting to consider the semi-hysteria that greeted Joyce O'Shaughnessy's 2009 ASCO plenary talk on the use of the PARP1 inhibitor, BSI-201, in metastatic triple-negative breast cancer when WINS demonstrated a relative reduction of 56 percent in recurrences and 64 percent in deaths in patients with ER/PR-negative tumors, and although we don't have HER2 assays in this older study, one can assume most were HER2-negative, thus triple-negative.

There are a number of potential explanations for why WINS and other similar data sets are not being followed up in spite of the dearth of current adjuvant trials in HER2-negative breast cancer and colon cancer. Top of the list is lack of industry interest in this type of research, which in my mind sort of means it won't get done because nowadays the somnolent NCI and maybe misdirected mammography-oriented advocacy groups don't seem to be executing a whole lot of practice-changing oncology research.

This issue is admittedly complicated, and there is justifiable pessimism about people altering their lifestyles along with the feeling that diet has as much to do with heart disease and other pathologies as neoplasia, thus "not our thing." However, translational

research can be done to begin to understand how changes to the human internal milieu and the ever-commented-on tumor microenvironment are correlated with nutritional intake and level of activity, and perhaps this will lead us to new or even existing targeted interventions, like insulin growth factor inhibitors, to get the job done.

Fans of our audio work may know how much this gripes me and I am constantly editing out large chunks of recorded conversations with my rants and raves about this issue, but the truth is that the public sector needs to get off its collective rear end and do something about it. In the interim, oncologists on the front lines owe it to their patients with breast cancer to let them know that in addition to surgery, radiation, chemo and biologics there may be something else they can do to further reduce the risk of recurrence.

Next up on the final issue of our 2009 San Antonio 5MJC, an eye-opening analysis from the historic MA17 trial demonstrating a profound reduction in risk of recurrence when an AI is used after five years of tamoxifen in patients who initially were premenopausal.

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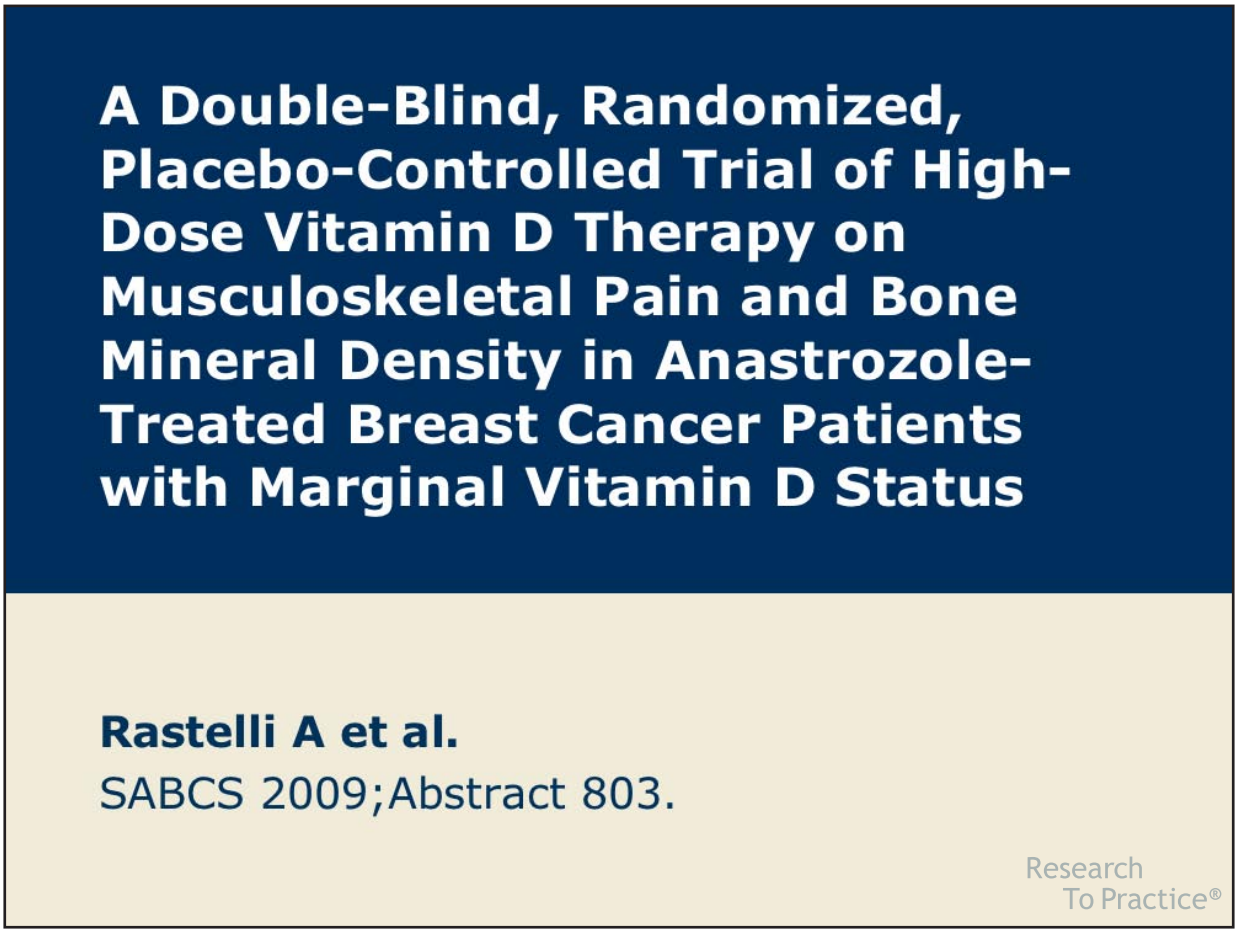
Effect of High-Dose Vitamin D Therapy on Bone Mineral Density and Anastrozole-Induced Musculoskeletal Pain

Presentation discussed in this issue

Rastelli AL et al. **A double-blind, randomized, placebo-controlled trial of high dose vitamin D therapy on musculoskeletal pain and bone mineral density in anastrozole-treated breast cancer patients with marginal vitamin D status.** San Antonio Breast Cancer Symposium 2009;**Abstract 803**.

Slides from a presentation at SABCS 2009 and transcribed comments from a recent interview with Rowan T Chlebowski, MD, PhD (1/15/10)



Introduction

- Musculoskeletal (MS) pain and bone loss are known adverse effects of aromatase inhibitors.
- A high prevalence of vitamin D deficiency/insufficiency has been previously reported in patients with breast cancer complaining of MS pain (SABCS 2004:Abstract 443).
- Anecdotal evidence suggests that MS pain induced by aromatase inhibitors can be relieved by weekly supplementation with high doses of vitamin D.
- **Current study objectives:**
  - Assess if high-dose vitamin D (HDD) supplementation improves anastrozole-induced musculoskeletal symptoms.
  - Assess if vitamin D supplementation may favorably impact the bone mineral density (BMD) of patients on anastrozole.

Rastelli A et al. SABCS 2009;Abstract 803.

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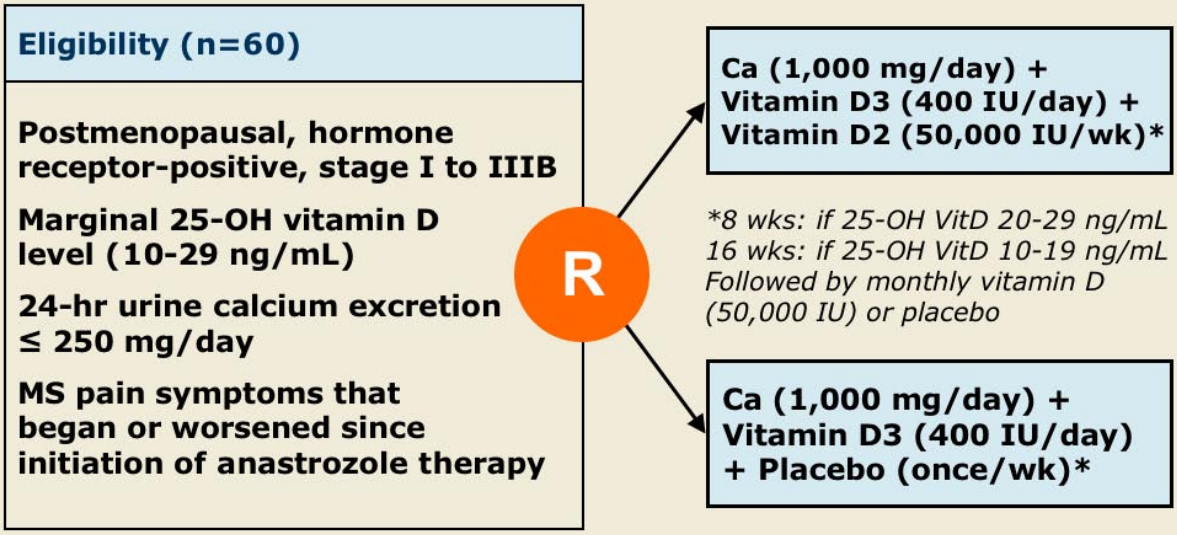
Trial Design



Pain and impairment evaluated: baseline, 2, 4, and 6 mos
Femoral/Neck BMD evaluated: baseline and 6 mos

Rastelli A et al. SABCS 2009;Abstract 803.

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Participants in Each Arm at Each Time Point

	High-dose Vitamin D	Placebo
Number of patients randomized	30	30
Number of discontinuations over 6 mos*	9	4
Number of patients completing 2 mos	28	29
Number of patients completing 4 mos	22	28
Number of patients completing 6 mos	21	26

**Reasons for discontinuation include: continued muscle pain, high serum or urinary calcium, or development of adverse event (Placebo arm: 1 diarrhea, 1 non-treatment related arterial thrombosis).*

Rastelli A et al. SABCS 2009;Abstract 803.

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Effect of High-Dose Vitamin D on Pain and BMD

- At 2 months, patients receiving HDD reported lower scores on pain-related questions on BPI (p=0.009) and FIQ surveys (p=0.01).
- A trend for improved scores for walking and climbing steps on the Health Assessment Questionnaire (HAQ) was reported in patients administered HDD (at 2 mos, p=0.04).
- Preliminary BMD analysis data demonstrated higher femoral/neck values in the HDD group (p=0.05).
  - HDD group, % change (0 - 6 mos): 0.54 ± 0.71
  - Placebo group, % change (0 - 6 mos): -1.43 ± 0.66

Rastelli A et al. SABCS 2009;Abstract 803.

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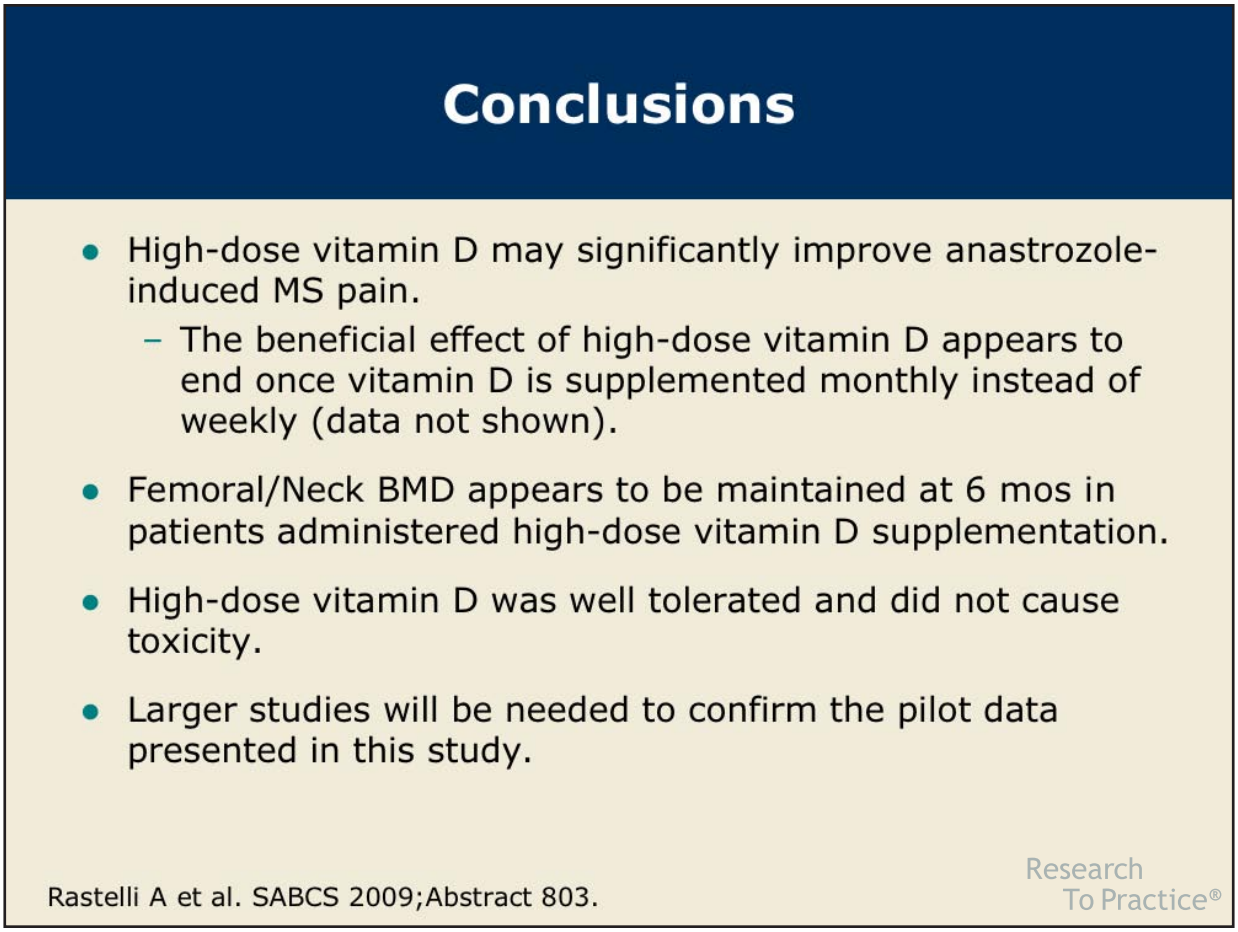

DR CHLEBOWSKI: Vitamin D is an interesting molecule and a lot of research is going on in this area. In the WINS study, we examined levels of 25-hydroxy vitamin D and found some increased evidence of joint problems among people in the lowest quintile. There was a study of a three-month trial in patients with fibromyalgia who received 50,000 international units of vitamin D per week for three months and didn't see an effect. The data are conflicting. I believe people are trying to obtain enough data to see if a definitive trial can be conducted, but there are questions to be addressed before we can go forward with that.

There appeared to be a short-term reduction in the reporting of musculoskeletal pain for a few months during weekly administration of high-dose vitamin D, and then the pain began to return with monthly therapy. This is an interesting signal, but I don't think it's an action item. I believe that there is an association between low vitamin D levels and outcome, but it isn't clear to me that replacement to any targeted level will change outcome.

I believe that vitamin D levels are determined genetically. When we examined 1,900 patients in the Women's Health Initiative in terms of vitamin D, we had good data on dietary intake and sunlight exposure. Patients in the highest quintile weren't taking much more vitamin D than patients in the lowest quintile. It would seem that differences in vitamin D levels are explained by something other than sunlight, dietary and supplement intake.

DR LOVE: Do you measure vitamin D in your patients in terms of cancer or bone health?

DR CHLEBOWSKI: No, I don't, but this is a controversial area. In terms of bone health, a meta-analysis released in the spring of last year concluded that there wasn't a clear association between vitamin D and fracture risk. However, a meta-analysis of all the randomized vitamin D replacement studies conducted mostly for osteoporosis showed that taking vitamin D resulted in a significant reduction in overall mortality. It's puzzling but perhaps encouraging at the same time.

Dr Chlebowski is Professor of Medicine at the David Geffen School of Medicine at UCLA and Chief of the Division of Medical Oncology and Hematology at Harbor-UCLA Medical Center in Torrance, California.