Management of Short- and Long-Term Toxicities of Aromatase Inhibitors

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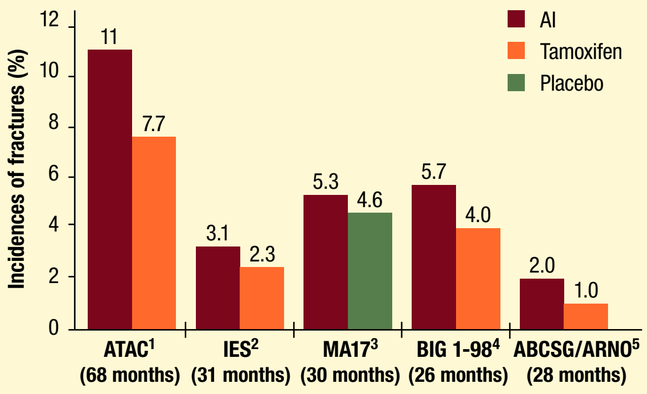
6

Musculoskeletal symptoms and bone loss are the two major adverse events of long-term adjuvant therapy with aromatase inhibitors (AIs), and both of these potential complications may be ameliorated. An Austrian study demonstrated that zoledronic acid can prevent bone loss in women treated with ovarian suppression and anastrozole. Bone density monitoring and bisphosphonates are now routinely used in patients receiving AIs. Arthralgias are common in breast cancer patients receiving tamoxifen, but the incidence increases with all AIs. A variety of oral and topical medications and nonpharmacologic approaches may improve arthralgias, which also tend to decrease with time on treatment. The spectrum of adverse AI events, including arthralgias, is similar regardless of whether patients received prior chemotherapy.

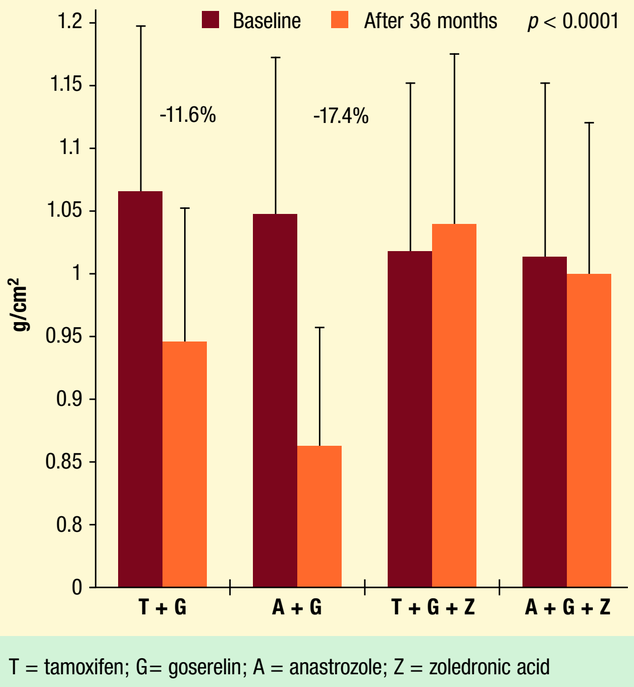
FRACTURES IN ADVJUVANT AI TRIALS



AI = Aromatase inhibitor; ATAC = Arimidex® (anastrozole), tamoxifen, alone or combination; IES = Intergroup exemestane study; MA17 = extended adjuvant treatment with letrozole trial; BIG 1-98 = IBCSG trial of letrozole versus tamoxifen; ABCSG/ARNO = combined Austrian-German trial

SOURCES: [1] Howell A et al. *Lancet* 2005;365(9453):60-2; [2] Coombes RC et al. *N Engl J Med* 2004;350(11):1081-92; [3] Goss PE et al. *J Natl Cancer Inst* 2005;97(17)1262-71; [4] Thürlimann B et al. Presentation. ASCO 2005; [5] Jakesz R et al. *Lancet* 2005;366(9484):455-62.

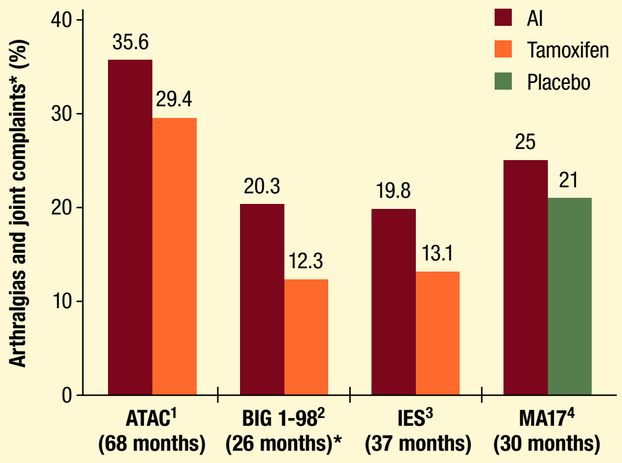
CHANGES IN BONE MINERAL DENSITY OF THE LUMBAR SPINE IN ABCSG-12



T = tamoxifen; G= goserelin; A = anastrozole; Z = zoledronic acid

SOURCE: Gnant M. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 6.

JOINT SYMPTOMS AND ARTHRALGIAS IN ADVJUVANT AI TRIALS



SOURCES: [1] Howell A et al. *Lancet* 2005;365(9453):60-2; [2] Thürlimann B et al. Presentation. ASCO 2005; [3] Plourde P et al. Poster. Lynn Sage Breast Cancer Symposium 2005; [4] Goss PE et al. *J Natl Cancer Inst* 2005;97(17)1262-71.

ATAC TRIAL: ADVERSE EVENTS IN PRIOR CHEMOTHERAPY AND NO CHEMOTHERAPY SUBGROUPS

	N	Relative risk ratio [anastrozole: tamoxifen] (95% CI)		
		Overall population	No prior chemotherapy	Prior chemotherapy
Endometrial cancer	18	0.20 (0.06, 0.69)	0.25 (0.07, 0.90)	0.00*
Fractures	356	1.60 (1.30, 1.97)	1.67 (1.32, 2.12)	1.36 (0.87, 2.11)
Hot flashes	2,328	0.87 (0.81, 0.93)	0.87 (0.81, 0.94)	0.86 (0.76, 0.98)
Ischaemic cerebro-vascular events	104	0.49 (0.32, 0.73)	0.50 (0.33, 0.77)	0.41 (0.13, 1.34)
Musculoskeletal disorders	1,668	1.28 (1.18, 1.40)	1.24 (1.13, 1.37)	1.38 (1.17, 1.62)
Vaginal bleeding	417	0.54 (0.45, 0.66)	0.55 (0.44, 0.68)	0.53 (0.35, 0.79)
Vaginal discharge	472	0.25 (0.20, 0.31)	0.24 (0.18, 0.31)	0.28 (0.18, 0.43)
Venous thrombo-embolic events	184	0.59 (0.44, 0.79)	0.63 (0.46, 0.86)	0.42 (019, 0.92)

N = total number of events

* There were no events for anastrozole in the prior chemotherapy subgroup.

SOURCE: Coleman R. Poster. European Society for Medical Oncology Congress 2004.

POTENTIAL INTERVENTIONS FOR ARTHRALGIAS

Pharmacologic approaches	Nonpharmacologic approaches
Oral treatments • Acetaminophen (≤4 g/day) • NSAID • COX-2 inhibitor • Tramadol • Opioids • Glucosamine • Chondroitin sulfate **Topical treatments** • Capsaicin • Methylsalicylate	• Self-management programs • Social support programs • Weight loss • Aerobic and muscle-strengthening exercises • Physical/occupational therapy • Heat • Patellar taping • Appropriate footwear and lateral wedged insoles • Joint protection

SOURCE: Plourde P et al. Poster. Lynn Sage Breast Cancer Symposium 2005.

SELECT PUBLICATIONS

Coleman R. **Association between prior chemotherapy and the adverse event profile of adjuvant anastrozole and tamoxifen: A retrospective analysis of data from the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial on behalf of the ATAC Trialists' Group.** Poster. European Society for Medical Oncology Congress 2004.

Coombes RC et al; Intergroup Exemestane Study. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92.

Gnant M. **Zoledronic acid effectively counteracts cancer treatment induced bone loss (CTIBL) in premenopausal women receiving adjuvant goserelin and tamoxifen or goserelin and anastrozole for hormone-responsive breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2004.

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA17.** *J Natl Cancer Inst* 2005;97(17):1262-71.

Howell A et al; ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2.

Jakesz R et al. **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial.** *Lancet* 2005;366(9484):455-62.

Plourde P et al. **Arthralgia in postmenopausal breast cancer patients on adjuvant endocrine therapy: A risk-benefit analysis.** Poster. Lynn Sage Breast Cancer Symposium 2005.

Thürlimann BJ et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** *Proc ASCO* 2005;Abstract 511.

AROMATASE INHIBITORS AND FRACTURES

The five-year overall toxicity data are very favorable for anastrozole compared to tamoxifen because the three life-threatening toxicities — endometrial cancer, arterial and venous vascular events — are all significantly less with anastrozole. Many oncologists have concern regarding bones, but I believe it's going to be not only a preventable, treatable situation but also something that is likely to go away completely in the near future. There is no difference in hip fractures after 68 months with anastrozole and tamoxifen. This is for a group of patients who had no prescreening when they entered the study and no ongoing protocol-defined follow-up for bone. If you're going to actually do any screening or treating, you're going to have lower numbers than that.

— Rowan T Chlebowski, MD, PhD. **Breast Cancer Update *2005 (7)***

The fracture rate incidence in ATAC is becoming a little more reassuring. An excess fracture rate occurs in the first two or three years, but then the lines begin to come together. As patients stop taking anastrozole, the fracture rate returns to that of the patients randomly assigned to tamoxifen. Furthermore, so far no difference has occurred in fractures of the neck or femur, which are of particular concern. I think the issue of bone is easy to manage. We should be alert to it, monitor bone mineral density, perhaps exclude patients who have established osteoporosis and then be ready to intervene with a bisphosphonate when the patient becomes osteopenic.

— Michael Baum, MD, ChM. **Breast Cancer Update *2005 (1)***

Great strides have been made in terms of the new bisphosphonates. The oral weekly preparations are well tolerated. I am optimistic that bone loss with aromatase inhibitors is completely manageable, and it may lead to a greater public health benefit by paving the way for having osteoporosis dealt with routinely in all postmenopausal women. That could be one of the more beneficial effects of this issue. With the new bisphosphonates and the potential availability of DEXA scans, osteoporosis may be a disease of the past in another decade.

— Jack Cuzick, PhD. **Breast Cancer Update *2005 (6)***

AROMATASE INHIBITORS AND MUSCULOSKELETAL DISORDERS

Arthralgia is a condition with effective available treatment options. Whereas the incidence of arthralgia reported in clinical trials is higher with anastrozole, the absolute difference compared with tamoxifen treatment is relatively small; this finding is similar for the other aromatase inhibitors, letrozole and exemestane… The variability in which this type of adverse event data is collected confounds the ability to make cross-trial comparisons and identify any potential differences in the occurrence of arthralgia among aromatase inhibitors… Better guidance is needed in the differential diagnosis of arthralgia, including consideration of other possible causes.

— Paul Plourde, MD et al. Poster. Lynn Sage Breast Cancer Symposium 2005.

Matt Ellis' group presented an interesting abstract at San Antonio indicating that women on aromatase inhibitors with these joint symptoms may have lowered vitamin D levels and that giving them vitamin D improved some of the joint symptoms. The data are very early, and they are conducting more studies, but if we could solve this joint problem with vitamin D, it would be extraordinary. We know from the ATAC trial that more serious adverse events are associated with tamoxifen than with anastrozole and that despite the joint symptoms, patients tend to stay on anastrozole more than they stay on tamoxifen, which is an important efficacy issue.

— Anthony Howell, MD. **Breast Cancer Update *2005 (4)***