Original Article

Osteoporosis Therapy and Outcomes for Postmenopausal Patients With Hormone Receptor–Positive Breast Cancer: NCIC CTG MA.27

Allan Lipton, MD[1]; Judith-Anne W. Chapman, PhD[2]; Kim Leitzel, MSc[1]; Ashwani Garg, MD[1]; Kathleen I. Pritchard, MD[3]; James N. Ingle, MD[4]; G. Thomas Budd, MD[5]; Matthew J. Ellis, MD, PhD[6]; George W. Sledge, MD[7]; Manuela Rabaglio, MD[8]; Lei Han, MSc[2]; Catherine R. Elliott, MSc[2]; Lois E. Shepherd, MD[2]; Paul E. Goss, MD, PhD[9]; and Suhail M. Ali, MD[1,10]

BACKGROUND: Breast cancer patients in the MA.27 trial had similar outcomes with steroidal aromatase inhibitor (AI) exemestane and nonsteroidal anastrozole. AIs increase the risk of osteoporosis. This study examined the effects of self-reported osteoporosis and osteoporosis therapy (OPT) on outcomes. **METHODS:** The MA.27 phase 3 adjuvant trial enrolled 7576 postmenopausal women. The primary outcome was event-free survival (EFS), and the secondary outcome was distant disease–free survival (DDFS). Patients were permitted bisphosphonates to prevent or treat osteopenia/osteoporosis. In a multivariate, stratified Cox regression, factors were significant with a 2-sided Wald test P value $\leq .05$. **RESULTS:** Osteoporosis was reported at the baseline by 654 of the 7576 women (8.6%) and in total by 1294 patients. Oral OPT was received at the baseline by 815 of the 7576 women (10.8%) and in total by 2711 patients (36%). With a median follow-up of 4.1 years, 693 EFS events (9.15%) and 321 DDFS events (4.2%) occurred. Osteoporosis was not associated with EFS or DDFS. Few EFS events occurred before the initiation of OPT, with no substantive evidence of a time-differing effect on outcomes (nonproportional hazards). OPT (yes vs no) was significantly associated with improved EFS (hazard ratio [HR] for yes vs no, 0.67; 95% confidence interval [CI], 0.57-0.80; $P < .001$) and DDFS (HR, 0.57; 95% CI, 0.44-0.73; $P < .001$). Time-differing (time-dependent) OPT was not (EFS; $P = .45$). OPT did not alter the incidence of visceral-only metastasis ($P = .31$). **CONCLUSIONS:** Oral OPT, administered to postmenopausal breast cancer patients receiving adjuvant AI therapy, was associated with improved EFS and DDFS; the time of OPT initiation (a time-dependent effect) did not affect the outcome. OPT did not alter the risk of visceral metastasis. ***Cancer*** **2017;000:000-000**. © *2017 American Cancer Society.*

KEYWORDS: adjuvant breast cancer, aromatase inhibitor, bisphosphonate, breast cancer, clinical outcome, osteoporosis, osteoporosis therapy.

INTRODUCTION

Stephen Paget is credited with proposing the seed and soil metastasis theory.[1] Osteoporosis is a bone disease with an increased fracture risk. An estrogen deficiency following menopause is associated with a rapid reduction in bone mineral density (BMD). In osteoporosis, BMD is reduced, the bone microarchitecture deteriorates, and the amount and variety of proteins released in the bone marrow microenvironment are altered.[2-4] The increased bone resorption associated with osteoporosis may provide fertile soil for cancer growth and accelerate the development of bone metastases.[5] We found in the NCIC Clinical Trials Group (CTG) MA.14 trial that higher baseline levels of bone resorption marker serum β-C-terminal telopeptide of type I collagen were associated with a shorter time to bone-only relapse.[6]

Bisphosphonates are used to treat or prevent bone loss,[7] including cancer treatment–induced bone loss due to aromatase inhibitors (AIs) and chemotherapy.[8,9] Bisphosphonates reduce skeletal complications from established bone

Corresponding author: Allan Lipton, MD, Division of Hematology/Oncology, Penn State Hershey Cancer Institute, Penn State Hershey Medical Center, 500 University Drive, Hershey, PA 17033; Fax: (717) 531-8796; alipton@hmc.psu.edu

[1]Penn State Hershey Cancer Institute, Penn State Hershey Medical Center, Hershey, Pennsylvania; [2]Canadian Cancer Trials Group, Queen's University, Kingston, Ontario, Canada; [3]Sunnybrook Odette Cancer Centre, Toronto Sunnybrook Regional Cancer Centre, Toronto, Ontario, Canada; [4]Oncology, Mayo Clinic, Rochester, Minnesota; [5]Taussig Cancer Center, Cleveland Clinic, Cleveland, Ohio; [6]Lester and Sue Smith Breast Center, Baylor College of Medicine, Houston, Texas; [7]Stanford University Medical Center, Stanford, California; [8]International Breast Cancer Study Group Coordinating Center and Inselspital, Bern, Switzerland; [9]Massachusetts General Hospital Cancer Center, Boston, Massachusetts; [10]Lebanon VA Medical Center, Lebanon, Pennsylvania.

See editorial on pages 000-000, this issue.

This study was presented at the 2012 Annual Meeting of the American Society of Clinical Oncology; June 1-5, 2012; Chicago, IL.

We acknowledge the assistance of Dr. Bingshu Chen in overseeing implementation of the reviewer-requested analyses.

The trial is registered with ClinicalTrials.gov (NCT00066573).

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.30682, **Received:** September 18, 2016; **Revised:** November 8, 2016; **Accepted:** December 1, 2016, **Published online** Month 00, 2017 in Wiley Online Library (wileyonlinelibrary.com)

metastases[8] and prevent the recurrence of early breast cancer.[10] A meta-analysis of 22,982 patients concluded that adjuvant bisphosphonate led to a 28% reduction in bone metastasis and an 18% reduction in breast cancer deaths among postmenopausal women.[11] Bisphosphonates may alter a hospitable bone microenvironment or have a direct antitumor effect.[12] However, bisphosphonates may increase the risk of visceral metastasis in perimenopausal females.[11]

We examined here whether osteoporosis therapy (OPT) affected outcomes in postmenopausal breast cancer patients treated with an adjuvant AI in the MA.27 trial.[13]

MATERIALS AND METHODS

Study Design

MA.27 is a cooperative-group, multicenter, multinational, randomized, open-label phase 3 trial of exemestane versus anastrozole.[13] Enrollment began in June 2003 after approval by health regulatory authorities and centers' institutional review boards and ended in 2008 (ClinicalTrials.gov identifier NCT00066573). MA.27 originally randomized postmenopausal women with receptor-positive primary breast cancer to exemestane or anastrozole with or without celecoxib (hypothesized to be an anticancer agent). Celecoxib was discontinued because of reports of cardiac toxicity.[14] Women enrolled during celecoxib assignment (n = 1622) were stratified by whether they were assigned to celecoxib and concomitant prophylactic aspirin use ($\leq$81 mg/d; n = 2209). In 2005, after positive results for an anti–human epidermal growth factor receptor 2 therapy, the protocol was amended to include stratification by trastuzumab (n = 1915).[15] The stratification factors in the full trial (n = 7576) were the lymph node status and the receipt of prior adjuvant chemotherapy. After providing informed consent, patients were assigned with a dynamic minimization algorithm[16] to open-label exemestane (25 mg daily) or anastrozole (1 mg daily). In the final analysis with a median follow-up of 4.1 years, there was no significant difference in event-free survival (EFS; hazard ratio [HR], 1.02; 95% confidence interval [CI], 0.87-1.18; $P = .85$) or distant disease–free survival (DDFS) between exemestane and anastrozole[13]; no further trial follow-up will occur.

MA.27 funding was provided by the Canadian Cancer Research Institute, the US National Cancer Institute, and Pfizer. Data were collected, managed, and analyzed by the Canadian Cancer Trials Group (formerly the NCIC CTG). The writing of the manuscript was undertaken by the authors.

Patient Population

Patient responses to questions about osteoporosis and OPT were obtained from MA.27 case report forms. In most instances, BMD reports were submitted and reviewed, although this information was not reported on MA.27 forms. Detailed BMD information was available only for 497 patients enrolled in the MA.27B substudy.[17] OPT was permitted during trial therapy except for patients with baseline T scores ≥ -2.0 who were enrolled in group A of the MA.27B bone substudy (300 patients).[17] Osteoporosis and bisphosphonate use were reported as prior or present at the baseline or were subsequently reported as a new diagnosis or (re-)introduction of therapy at planned intervals of 6 and 12 months and then yearly thereafter. The length of the prior OPT therapy was unknown. Concomitant medications were collected at the baseline and throughout the study. In most cases but not all, the oral bisphosphonates used were noted. Intravenous bisphosphonates were not routinely used in this population. Osteoporosis and OPT were of interest in the adjuvant setting, so we restricted reporting to be at the baseline or at follow-up more than 30 days before disease recurrence. OPT had a variable duration and discretionary administration.

Study Endpoints

The primary endpoint for the MA.27 trial and this study was EFS, which was defined as the time from randomization to locoregional or distant disease recurrence, new primary breast cancer, or death from any cause; censoring was at the longest follow-up. A secondary endpoint for both the MA.27 trial and this analysis was DDFS, which was defined as the time from randomization to distant disease recurrence beyond the breast or regional lymph nodes or death with or due to breast cancer; censoring was performed at the time of death from other causes or longest follow-up. We also considered the time to bone-only relapse, bone relapse concurrent with other relapse, and nonbone recurrence. One DDFS bone marrow–only recurrence was excluded. Disease recurrence was defined pathologically or was based on clinical or radiologic findings, and recurrences were dated at the time that they were first detected. Recurrence was always based on the onset of a sign and never based on the onset of a symptom.

Statistical Analysis

Investigations of the effect of OPT on outcomes could be substantively biased for those who started OPT during the

TABLE 1. Patient Characteristics

	Exemestane, No. (%)	Anastrozole, No. (%)	Total, No. (%)
Total	3789 (100)	3787 (100)	7576 (100)
Age < 70 y	2699 (71)	2718 (72)	5417 (72)
Race: white	3593 (95)	3558 (94)	7151 (94)
ECOG PS: 0 or 1	3755 (99)	3761 (99)	7516 (99)
Partial mastectomy	2609 (69)	2554 (67)	5163 (68)
Axillary dissection	1944 (51)	1955 (52)	3899 (52)
T1	2710 (72)	2718 (72)	5428 (72)
N0	2693 (71)	2678 (71)	5371 (71)
Adjuvant chemotherapy	1163 (31)	1164 (31)	2327 (31)
Radiotherapy	2717 (72)	2663 (70)	5380 (71)
Fractures within 10 y	383 (10)	361 (10)	744 (10)
Cardiovascular disease	2006 (53)	2068 (55)	4074 (54)
Osteoporosis > 30 d before 1st relapse	639 (17)	655 (17)	1294 (17)
Osteoporosis therapy > 30 d before 1st relapse	1290 (34)	1421 (38)	2711 (36)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.

trial because of differences in population characteristics due to higher risk patient attrition by outcome events. The likelihood of a sizable bias depended on the timing and rates of the competing risks of starting OPT and having an event. We examined a timeline plot of the number of patients who had taken OPT and had EFS events. To examine changes in the population risk over time, we examined the assumption of proportional hazards for receiving OPT > 30 days before relapse with a plot of the logarithm of cumulative hazards against time. Landmarking was not used in this analysis because MA.27 had a low EFS event rate during a median follow-up of 4.1 years.[18] Instead, we looked at the multivariate effect of OPT started > 30 days before relapse in 4 ways: 1) yes versus no, 2) length of OPT in years (capped at trial follow-up for those with prior OPT use), 3) yes versus no for time-dependent OPT (a woman who started OPT during trial follow-up was classified as no until she started therapy), and 4) exploratory analysis for those who were taking OPT at the baseline.

Analyses used the intention-to-treat population. All tests were 2-sided, with significance indicated by an unadjusted P value $\leq .05$. Analyses were performed with SAS software (version 9.2; SAS Institute, Inc). As stratification factors, the lymph node status (negative, positive, or unknown), prior adjuvant chemotherapy (yes vs no), and the use of celecoxib (yes vs no), prophylactic aspirin (yes vs no), and trastuzumab (yes vs no) were used here in stratified analyses during the periods in which they were operative. An univariate assessment was performed with a stratified log-rank test and described with a Kaplan-Meier plot. Multivariate assessments were performed with exploratory stepwise forward stratified Cox regression with osteoporosis and OPT as defined previously, MA.27 treatment (exemestane vs anastrozole), and baseline patient characteristics (age [$\leq$69 vs $\geq$70 y], race [white vs nonwhite], Eastern Cooperative Oncology Group performance status [0 or 1 vs other], surgery [partial mastectomy vs mastectomy], pathologic T stage [T1 vs $\geq$T2], adjuvant radiotherapy [yes vs no], fractures within past 10 years [yes vs no], and cardiovascular disease [yes vs no]). A factor was added to a multivariate model if the 2-sided Wald test had a P value $\leq .05$.

RESULTS

Patients who joined the NCIC CTG MA.27 trial had a median age of 64 years. Other baseline characteristics were similar between the treatment arms (Table 1). Overall, this was a low-risk population of breast cancer patients; 72% had T1 tumors, 71% were node-negative, and only 31% received adjuvant chemotherapy. The mean body mass index for all patients was 29.3 kg/m^2 (27.2 kg/m^2 for those receiving baseline OPT and 27.9 kg/m^2 for those who ever received OPT).

Osteoporosis was self-reported at the baseline by 654 of 7576 women (8.6%); with new reports more than 30 days before relapse, the total number came to 1294 (17%; see the Consolidated Standards of Reporting Trials diagram in Fig. 1). Of the 1294 patients reporting osteoporosis, 1101 (85%) reported receiving OPT; 193 (15%) did not (Fig. 1). Baseline OPT was reported by 815 of 7576 women (10.8%); in total, 2711 patients (36%) received OPT (1610 [26%] presumably for osteopenia or as prophylaxis), whereas 4672 of the 6282 women without osteoporosis (74%) did not (Fig. 1).

The administration of OPT began rapidly in the first few years of the trial, with 2711 women (36%) receiving OPT, whereas the total number of EFS events during

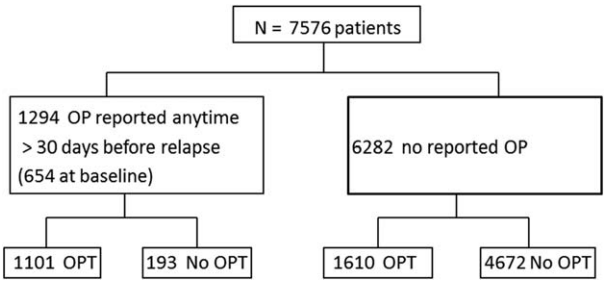

Figure 1. Consolidated Standards of Reporting Trials diagram for OP and OPT. Both OP and OPT occurred more than 30 days before relapse. OP indicates osteoporosis; OPT, osteoporosis therapy.

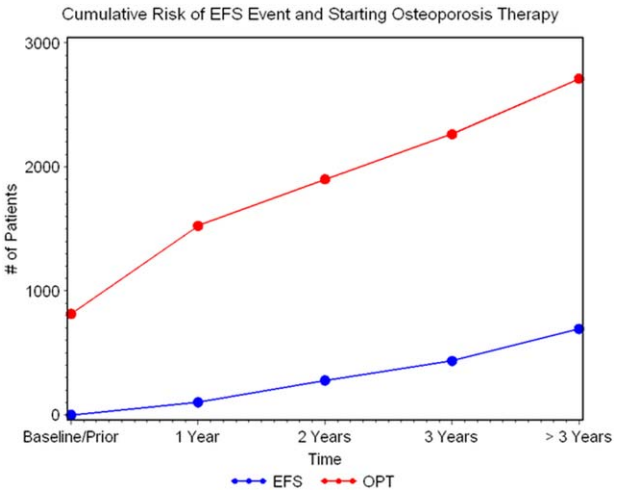

Figure 2. Timeline for patients starting OPT and cumulative number of EFS events. EFS indicates event-free survival; OPT, osteoporosis therapy.

the trial was low (9.15%). Figure 2 has a timeline plot of OPT patient counts and the number of EFS events during the same time period; 815 women began before or at the baseline, with 116 patients having had prior exposure to raloxifene. Another 39 patients began taking raloxifene during the study. All other patients were treated with bisphosphonates. There was no evidence of nonproportional hazards, with those patients receiving OPT maintaining substantively better EFS throughout the follow-up than those who did not (Fig. 3).

In the MA.27 trial of 7576 women, 693 (9.15%) had EFS events; 321 patients (4.2%) had DDFS events (1 had an unspecified type of DDFS, and 1 bone marrow–only relapse was excluded); 106 (1.4%) had bone-only relapse; 107 (1.4%) had bone relapse concurrent with other relapse; and 106 (1.4%) had nonbone relapse. OPT did not alter the incidence of visceral-only metastasis

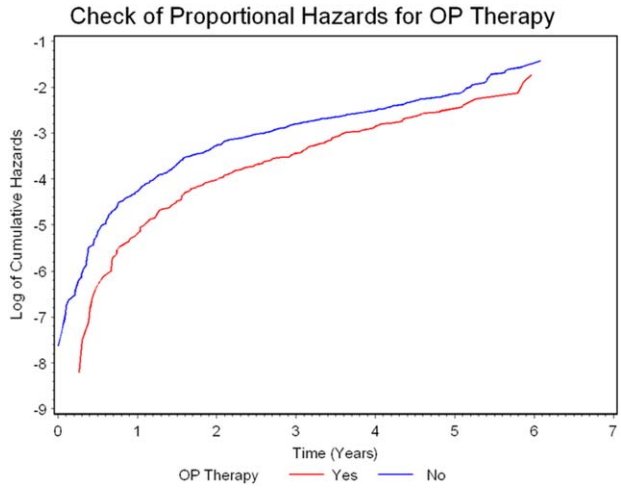

Figure 3. Logarithm of the cumulative hazard of event-free survival by OP therapy (yes vs no) more than 30 days before relapse. OP indicates osteoporosis.

(Supporting Table 1 [see online supporting information]): for all patients administered OPT, the rate was 1.22% with OPT versus 1.50% with no OPT ($P = .31$), and for patients taking OPT at the baseline, the rate was 1.8% with OPT versus 1.3% with no OPT ($P = .26$).

In the univariate analysis, osteoporosis was not associated with EFS (HR for yes vs no, 0.95; 95% CI, 0.77-1.16; $P = .60$) or DDFS (HR, 0.78; 95% CI, 0.57-1.08; $P = .13$). Osteoporosis was not significantly associated in multivariate analyses with EFS, DDFS, or relapse in the bone with or without relapse in other sites or nonbone relapse.

In the univariate analysis, the 815 patients who took OPT at the baseline did not have a significantly different EFS experience than the other 6761 MA.27 patients (HR for yes vs no, 0.95; 95% CI, 0.75-1.21; $P = .69$). However, women who received OPT (n = 2711), whether or not they had osteoporosis, had better EFS than patients who did not receive OPT (HR for yes vs no, 0.70; 95% CI, 0.59-0.83; $P <. 001$); the absolute 5-year rate improvement was 4% (from 87% [95% CI, 86%-88%] without OPT to 91% [95% CI, 89%-92%] with OPT; Fig. 4A). Cross-tabulation of the receipt of baseline OPT therapy by subcomponents of the EFS endpoint showed that with OPT, there was a lower likelihood of developing bone metastases with other metastases ($P = .02$); similar results were seen for those who had ever received OPT therapy, with additional reductions in locoregional recurrence, contralateral breast cancer, or bone metastasis alone (Supporting Table 1 [see online supporting information]). OPT was not significantly associated with other causes of

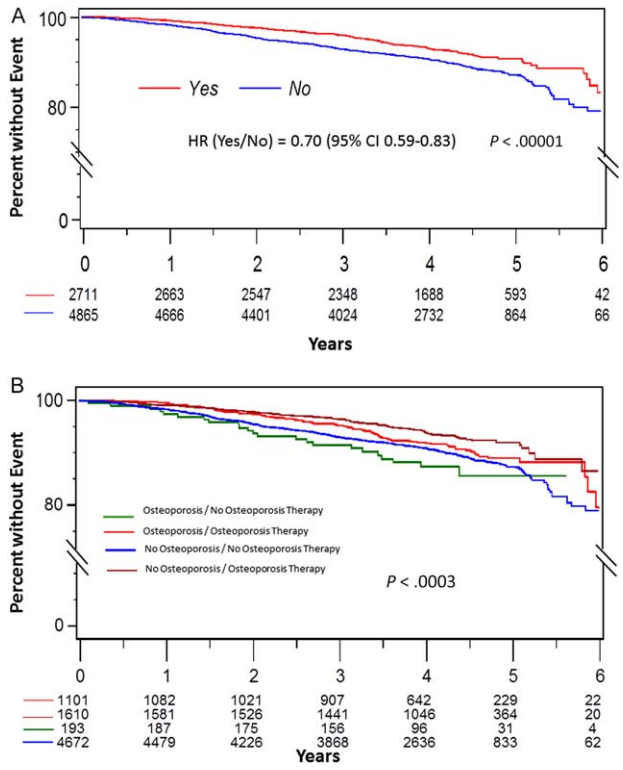

Figure 4. (A) Kaplan-Meier plot of event-free survival by osteoporosis therapy (yes vs no). Osteoporosis occurred more than 30 days before relapse. (B) Kaplan-Meier plot of event-free survival by osteoporosis and osteoporosis therapy. Both osteoporosis and osteoporosis therapy occurred more than 30 days before relapse. CI indicates confidence interval; HR, hazard ratio.

death. Patient outcomes differed significantly when they were examined by osteoporosis status and receipt of OPT ($P < .001$; Fig. 4B). Patients with osteoporosis who received OPT (5-year EFS, 89%; 95% CI, 86%-91%) had 3% better EFS than those with osteoporosis who did not receive OPT (EFS, 86%; 95% CI, 78%-91%) with an HR of 0.63 (95% CI, 0.40-1.00; Fig. 4B). Similarly, patients without osteoporosis who received OPT (5-year EFS, 92%; 95% CI, 90%-93%) had 5% better EFS than patients without osteoporosis who did not receive OPT (EFS, 87%; 95% CI, 86%-89%) with an HR of 0.65 (95% CI, 0.61-0.68; Fig. 4B).

Similar results were seen with DDFS. The dual consideration of osteoporosis and receipt of OPT had a univariate association with DDFS ($P < .001$). Osteoporotic patients had better DDFS if they received OPT (HR, 0.52; 95% CI, 0.26-1.06) with a 5-year improvement of 2% (from 94% [95% CI, 88%-97%] without OPT to 96% [95% CI, 95%-97%] with OPT). Similarly, patients without osteoporosis who received OPT had better DDFS than patients without osteoporosis who did not receive OPT (HR, 0.54; 95% CI, 0.50-0.59) with a 5-year rate improvement of 3% (from 93% [95% CI, 92%-94%] to 96% [95% CI, 95%-97%]).

The multivariate analysis indicated that OPT begun more than 30 days before relapse was associated with better EFS (HR for yes vs no, 0.67; 95% CI, 0.57-0.80; $P <$. 001), as was the length of OPT during the trial (HR, 0.79; 95% CI, 0.75-0.84; $P <$. 001; Table 2). However, there was no such indication with osteoporosis as a time-dependent factor (HR for yes vs no, 1.07; 95% CI, 0.90-1.26; $P = .45$). Similarly, OPT was significantly associated with DDFS (HR for yes vs no, 0.57; 95% CI, 0.44-0.73; $P <$. 001) and the length of OPT, although it was not with time-dependent OPT. Interactions of OPT and trial AI therapy were not significant.

DISCUSSION

Osteoporosis globally affects more than 200 million people, 10 million of whom are in the United States. One of every 2 women older than 50 years will have an osteoporosis-related fracture in her lifetime.[19,20] Increased bone resorption occurring in osteoporosis and osteopenia may increase bone metastasis growth in breast cancer. AIs increase the risk of osteoporosis by decreasing estrogen levels; this leads to increased bone resorption and a higher risk of fragility fractures in comparison with tamoxifen. Currently, bisphosphonates and denosumab are used clinically to prevent cancer treatment–induced bone loss.[8,9] The largest prospective bone study to date (NCIC MA.27B with 497 patients) reported that bisphosphonate use prevented aromatase-induced bone loss in women with osteoporosis,[17] and this confirmed similar results in previous reports.[21-23] Here, osteoporosis alone was not associated with EFS, DDFS, or relapse in bone, although this result may have been attenuated by the fact that only 85% of the osteoporotic women were being treated with OPT.

There is now a large body of clinical evidence showing that bisphosphonates reduce the risk of disease recurrence in early-stage breast cancer patients; the hypothesis is that bisphosphonates improve disease-free and overall survival. Recent phase 3 trials with oral clodronate[24] and zoledronic acid (AZURE trial)[25] showed that bisphosphonates significantly decreased relapse and death in patients for whom menopause had occurred at least 5 years earlier. However, pre- and perimenopausal patients in the AZURE study had a higher incidence of visceral metastasis and shorter overall survival with zoledronic acid treatment.[25] In the Austrian Breast and Colorectal Cancer

TABLE 2. EFS Multivariate Stepwise Cox Model With Osteoporosis Therapy

Factor	Model[a]	Osteoporosis Therapy		
		HR	95% CI	*P*[b]
Exemestane vs anastrozole	1	1.01	0.87-1.18	.87
	2	1.01	0.87-1.17	.90
	3	1.03	0.88-1.19	.75
Age: ≥70 vs ≤69 y	1	1.62	1.37-1.92	<.001
	2	1.66	1.40-1.97	<.001
	3	1.58	1.33-1.87	<.001
ECOG PS: other vs fully active or 1	1	2.91	1.70-4.99	<.001
	2	2.78	1.62-4.77	<.001
	3	2.92	1.70-5.00	<.001
Mastectomy vs partial mastectomy	1	1.24	1.06-1.46	.01
	2	1.24	1.06-1.46	.01
	3	1.22	1.03-1.43	.02
≥T2 vs T1	1	1.75	1.47-2.07	<.001
	2	1.71	1.44-2.03	<.001
	3	1.78	1.50-2.10	<.001
Prior adjuvant chemotherapy: yes vs no	1	0.29	0.12-0.69	.01
	2	0.29	0.12-0.69	.01
	3	0.28	0.12-0.68	.005
Prior fracture: yes vs no	1	1.40	1.11-1.75	.004
	2	1.46	1.17-1.84	.001
	3	1.32	1.06-1.66	.02
Osteoporosis therapy > 30 d before 1st relapse	1	0.67	0.57-0.80	<.001
	2	0.79	0.75-0.84	<.001
	3	1.07	0.90-1.26	.45

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PS, performance status.
[a] Model 1 is the model with osteoporosis therapy (yes vs no); model 2 is the model with the length of osteoporosis therapy (years), and model 3 is the model with time-dependent osteoporosis therapy (yes vs no).
[b] *P* values are based on a 2-sided Wald test.

Study Group (ABCSG) 12 trial of adjuvant zoledronic acid in premenopausal women with early-stage breast cancer, a disease-free survival benefit was found for the older premenopausal patients.[26] In the postmenopausal cohort (11,766 patients) of the Oxford meta-analysis (22,982 patients), adjuvant bisphosphonate use reduced bone metastases by 28% and breast cancer deaths by 18%, with similar benefits from aminobisphosphonates and clodronate.[11] There was no reduction in the first distant recurrence outside bone; there was no effect on premenopausal patients; and there were no effects on non–breast cancer deaths, contralateral breast cancer, or locoregional recurrence.[11] A xenograft report confirmed that zoledronic acid had inhibitory antitumor activity only in the postmenopausal bone microenvironment; MDA-MB-231 tumor growth in bone was inhibited by an osteoclast-mediated mechanism in the postmenopausal (ovariectomy) model but not in the premenopausal (sham) model.[27]

Our study assessed postmenopausal patients with hormone receptor–positive, early-stage breast cancer and the effect of OPT administered in conjunction with adjuvant AI therapy. Our MA.27 trial data for the first time assessed the use of OPT in postmenopausal, hormone receptor–positive patients, regardless of whether the patients did or did not have osteoporosis. More than half of the MA.27 OPT recipients did not have osteoporosis. Thus, one might postulate that OPT was frequently being administered prophylactically to patients, and this, not a guarantee-time bias, led to our observed consistent indication of OPT patients having a better experience over time. The overall good experience of the MA.27 patients precluded landmarked investigations, and the trial was underpowered for further analytic patient subgrouping.

In this study, patients reported a diagnosis of osteoporosis and/or OPT at variable times after their enrollment in the study. Because of the different times at which the diagnosis of osteoporosis was made and/or OPT was started, several statistical methods were used to estimate the effects of osteoporosis and OPT. The models obtained different results. The number of EFS events before the initiation of OPT was low; there was no evidence of a time-differing effect on outcomes (nonproportional hazards), with patients receiving OPT maintaining better EFS throughout follow-up in comparison with those who did not receive it. Only non–time-dependent OPT and the

length of OPT had significant multivariate associations with outcomes. Time-dependent OPT (a differing effect) did not. Similar results were seen for DDFS.

Studies have evaluated the use of bisphosphonates in patients without osteoporosis in the adjuvant setting with the aim of decreasing the incidence of bone metastasis. Concerns about an increased incidence of visceral metastasis were raised in 2 studies.[25,28] In one, the increase in visceral metastasis was limited to perimenopausal patients.[25] Postmenopausal MA.27 patients did not have an altered incidence of visceral metastasis.

There are several limitations to our study. The MA.27 trial was designed to test the impact of 2 AIs on patient outcomes with stratification by factors that could affect this assessment; concurrent information about the bone status such as prior fractures, osteoporosis, and OPT were not a part of the MA.27 trial design, although they appeared similar at the baseline by trial arm, and data were prospectively gathered during follow-up about the subsequent development of osteoporosis and (re-)initiation of OPT. Detailed knowledge of a patient's BMD was available only for the 497 patients who were enrolled in the MA.27B bone substudy.[17] The duration of OPT was variable. The MA.27 patient population was predominantly low-risk; 9.15% of the patients had an EFS event within a median of 4.1 years, with 4.2% having a distant relapse. The low event rates precluded a robust examination of subgroup experience and a landmarked analysis. However, the rapid uptake of OPT by 36% of the population would have been expected to minimize bias due to infrequent early events. There was no evidence showing that the receipt of OPT had a differing effect on outcomes throughout follow-up (nonproportional hazards); time-dependent OPT (a differing effect) did not have a significant multivariate association with outcomes. The 815 baseline OPT users did not have an experience significantly different from that of other MA.27 patients, including the 1896 patients who began OPT shortly thereafter; again, the low MA.27 relapse rate and the short median follow-up of 4.1 years pose a limitation for these investigations.

Osteoporosis was self-reported, although mostly confirmed with BMD reports; it is unclear why 15% of the patients with osteoporosis did not receive OPT. Finally, our study accrued only postmenopausal women with hormone receptor–positive breast cancer. Investigations would be needed to determine the applicability to receptor-negative breast cancer. An ongoing trial of adjuvant denosumab has a broader population of both pre- and postmenopausal patients (D-CARE; ClinicalTrials.gov identifier NCT01077154).

Multiple reports in the last decade have suggested that the adjuvant use of bisphosphonates can improve outcomes for patients with early breast cancer. Indeed, in a recent Oxford meta-analysis,[11] the use of bisphosphonates resulted in fewer bone relapses in patients with late postmenopausal breast cancer. In our study, in postmenopausal patients with hormone receptor–positive breast cancer, the receipt of oral OPT more than 30 days before relapse and the length of OPT were associated with improved outcomes; the effect of OPT by the time of initiation (a time-dependent effect) was not significantly associated with outcomes. The conclusion of the Oxford meta-analysis[11] as well as the most recent European consensus panel report[29] is that postmenopausal adjuvant breast cancer patients should be offered bisphosphonate treatment, with a majority of panelists (58%) restricting bisphosphonate use to those patients at intermediate or high risk for recurrence. Most recently, the results of the ABCSG-18 trial of adjuvant denosumab may expand this conclusion because denosumab has been reported to not only decrease the time to first clinical fracture (HR, 0.50; $P < .0001$)[30] but also increase disease-free survival in postmenopausal adjuvant breast cancer patients treated with a nonsteroidal AI.[31]

In conclusion, this study provides no contraindication to the use of oral OPT in women with localized breast cancer. OPT was not associated with an alteration in visceral-only metastasis here. This study adds to the growing body of literature concerning the benefits of adjuvant bisphosphonate therapy. A prospective study of adjuvant oral bisphosphonate therapy is needed to confirm these results.

FUNDING SUPPORT

This work was supported by the Canadian Cancer Society Research Institute (grant 015469), the Cancer Therapy Evaluation Program of the National Cancer Institute at the National Institutes of Health (grants 2U10CA077202 and CA32102), and Pfizer New York, Canada. Paul E. Goss is supported by the Avon Foundation (New York, NY).

CONFLICT OF INTEREST DISCLOSURES

Kathleen I. Pritchard reports grants and personal fees from AstraZeneca, Pfizer, Roche, Novartis, and Eisai and personal fees from Amgen and GlaxoSmithKline outside the submitted work. Matthew J. Ellis reports ad hoc consulting for AstraZeneca, Pfizer, Novartis, Celgene, and Puma. Ellis also notes a patent licensed to Prosigna/NanoString by Bioclassifier LLC; he is the chief executive officer of Bioclassifier and receives royalty payments.

AUTHOR CONTRIBUTIONS

Allan Lipton: Conceptualization, methodology, writing–original draft, writing–review and editing, supervision, and project administration. **Judith-Anne W. Chapman:** Conceptualization, methodology, validation, formal analysis, investigation, data curation, writing–original draft, writing–review and editing, visualization, and supervision. **Kim Leitzel:** Conceptualization, writing–original draft, writing–review and editing, and visualization. **Ashwani Garg:** Data curation, writing–review and editing, and visualization. **Kathleen I. Pritchard:** Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–review and editing, and supervision. **James N. Ingle:** Resources and writing–review and editing. **G. Thomas Budd:** Conceptualization, methodology, investigation, resources, writing–review and editing, and supervision. **Matthew J. Ellis:** Conceptualization, methodology, investigation, resources, and writing–review and editing. **George W. Sledge:** Conceptualization, writing–review and editing, and supervision. **Manuela Rabaglio:** Writing–review and editing. **Lei Han:** Software and writing–review and editing. **Catherine R. Elliott:** Methodology, investigation, writing–review and editing, and project administration. **Lois E. Shepherd:** Conceptualization, methodology, validation, data curation, writing–review and editing, and supervision. **Paul E. Goss:** Conceptualization, methodology, investigation, and writing–review and editing. **Suhail M. Ali:** Conceptualization, methodology, formal analysis, writing–original draft, writing–review and editing, and visualization.

REFERENCES

1. Paget S. The distribution of secondary growths in cancer of the breast. *Lancet.* 1889;133:571-573.
2. Frost HM. Bone Remodeling Dynamics. Springfield, IL: Charles C. Thomas; 1963.
3. Raisz L. Pathogenesis of osteoporosis: concepts, conflicts and prospects. *J Clin Invest.* 2005;115:3318-3325.
4. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature.* 2003;423:337-342.
5. Kakonen SM, Mundy GR. Mechanisms of osteolytic bone metastases in breast carcinoma. *Cancer.* 2003;97(3 suppl):834-839.
6. Lipton A, Chapman JW, Demers L, et al. Elevated bone turnover predicts for bone metastasis in postmenopausal breast cancer: results of NCIC CTG MA.14. *J Clin Oncol.* 2011;29:3605-3610.
7. Iannitti T, Rosini S, Lodi D, et al. Bisphosphonates: focus on inflammation and bone loss. *Am J Ther.* 2012;19:228-246.
8. Hadji P, Gnant M, Body JJ, et al. Cancer treatment–induced bone loss in premenopausal women: a need for therapeutic intervention? *Cancer Treat Rev.* 2012;38:798-806.
9. Coleman RE, Rathbone E, Brown JE. Management of cancer treatment–induced bone loss. *Nat Rev Rheumatol.* 2013;9:365-374.
10. Gnant M. Role of bisphosphonates in postmenopausal women with breast cancer. *Cancer Treat Rev.* 2014;40:476-484.
11. Coleman RE, Gnant M, Paterson A, et al; EBCTCG Bisphosphonate Working Group. Adjuvant bisphosphonate treatment in early breast cancer: meta-analysis of individual patient data from randomized trials. *Lancet.* 2015;386:1353-1361.
12. Gnant M, Clezardin P. Direct and indirect anticancer activity of bisphosphonates: a brief review of published literature. *Cancer Treat Rev.* 2012;38:407-415.
13. Goss PE, Ingle JN, Pritchard KI, et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27—a randomized controlled phase III trial. *J Clin Oncol.* 2013;31:1398-1404.
14. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med.* 2005;352:1071-1080.
15. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.* 2005;353:1673-1684.
16. Tu D. Minimization procedure. In: Chow SC, ed. Encyclopedia of Biopharmaceutical Statistics. 3rd ed. New York, NY: Marcel Dekker; 2010:795-798.
17. Goss PE, Hershman DL, Cheung AM, et al. Effects of adjuvant exemestane versus anastrozole on bone mineral density for women with early breast cancer (MA.27B): a companion analysis of a randomized controlled trial. *Lancet Oncol.* 2014;15:474-482.
18. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. *J Clin Oncol.* 2013;31:2963-2969.
19. National Osteoporosis Foundation. 1996 and 2015 Osteoporosis Prevalence Figures: State-by-State Report. Arlington, VA: National Osteoporosis Foundation; 1997.
20. Scott LJ. Denosumab: a review of its use in postmenopausal women with osteoporosis. *Drugs Aging.* 2014;31:566-576.
21. Van Poznak C, Hannon RA, Mackey JR, et al. Prevention of aromatase inhibitor–induced bone loss using risedronate: the SABRE trial. *J Clin Oncol.* 2010;28:967-975.
22. Lester JE, Dodwell D, Brown JE, et al. Prevention of anastrozole induced bone loss with monthly oral ibandronate: final 5 year results from the ARIBON trial. *J Bone Oncol.* 2012;1:57-62.
23. Lomax AJ, Yap SY, White K, et al. Prevention of aromatase inhibitor–induced bone loss with alendronate in postmenopausal women: the BATMAN Trial. *J Bone Oncol.* 2013;2:145-153.
24. Paterson AH, Anderson SJ, Lembersky BC. Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): a multicentre, placebo-controlled, randomised trial. *Lancet Oncol.* 2012;13:734-742.
25. Coleman RE, Cameron D, Dodwell D, et al. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG01/04) randomized open-label phase 3 trial. *Lancet Oncol.* 2014;15:997-1006.
26. Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol.* 2011;12:631-641.
27. Ottewell PD, Wang N, Brown HK, et al. Zoledronic acid has differential antitumor activity in the pre- and postmenopausal bone microenvironment in vivo. *Clin Cancer Res.* 2014;20:2922-2932.
28. Saarto T, Blomqvist C, Virkkunen P, et al. Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. *J Clin Oncol.* 2001;19:10-17.
29. Hadji P, Coleman RE, Wilson C, et al. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European panel. *Ann Oncol.* 2016;27:379-390.
30. Gnant M, Pfeiler G, Dubsky PC, et al, Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet.* 2015;386:433-443.
31. Gnant M, Pfeiler, G, Dubsky PC, et al. The impact of adjuvant denosumab on disease-free survival: results from 3,425 postmenopausal patients of the ABCSG-18 trial [abstract S2-02]. *Cancer Res.* 2016;76(4 suppl):S2-02.