



CED-CCO Special Advice Report #16

Zoledronic Acid as Adjuvant Therapy in Combination with Adjuvant Endocrine Therapy for Premenopausal Women with Early-Stage Hormone Receptor Positive Breast Cancer

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SUMMARY

The full CED-CCO Special Advice Report #16 consists of a Summary and a Full Report and is available on the CCO website (<http://www.cancercare.on.ca>)
PEBC CED-CCO page at:

<http://www.cancercare.on.ca/toolbox/qualityguidelines/other-reports/evaldrug-rep/>

QUESTIONS

1. Does the use of adjuvant zoledronic acid in combination with adjuvant endocrine therapy in premenopausal women with early-stage hormone-receptor-positive breast cancer result in improved outcomes? Outcomes of interest include overall survival (OS), disease-free survival (DFS), recurrence rate, fragility fractures, and adverse events.
2. Which subgroups of patients benefit the most from adjuvant zoledronic acid?
3. What is the optimal dose and schedule of adjuvant zoledronic acid?

TARGET POPULATION

Premenopausal women with early-stage hormone-receptor-positive breast cancer.

RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report.

- **There is insufficient evidence to recommend the routine use of adjuvant zoledronic acid in combination with adjuvant endocrine therapy as was given in the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 trial (1) to premenopausal women with early-stage breast cancer.**

QUALIFYING STATEMENTS

- When premenopausal women with hormone-sensitive breast cancer are treated with gonadotropin-releasing hormone (GnRH) agonist analogues and either tamoxifen or anastrozole for three years, the addition of zoledronic acid every six months for three years is associated with significant improvements in DFS and bone mineral density (BMD) (1).
- The routine use of either a GnRH analogue with tamoxifen or a GnRH analogue with anastrozole would not be considered standard of care in this setting (see related guidelines: Breast Cancer Disease Site Group Evidence-based Series #1-9: *Adjuvant Ovarian Ablation in the Treatment of Women with Early Stage Invasive Breast Cancer*).
- The total duration of systemic therapy in this study was only three years, which would be considered suboptimal in most global settings.
- In this special advice report, we specifically define adjuvant endocrine therapy as the systemic therapy given after local therapy (i.e., surgery/radiotherapy) to help decrease the risk of the cancer recurring. This risk of recurrence is reflected through OS, DFS (time from randomization to local recurrence, contralateral carcinoma, distant metastasis, secondary carcinoma, and/or death), and or recurrence-free survival (time from randomization to local relapse, contralateral carcinoma, distant metastasis, and/or secondary carcinoma).

KEY EVIDENCE

A single multicentre trial randomized patients to goserelin/tamoxifen (n=451), goserelin/tamoxifen/zoledronic acid (n=449), goserelin/anastrozole (n=453), or to goserelin/anastrozole/zoledronic acid (n=450) (1). When comparing patients who received zoledronic acid to those who did not, there was no significant difference in the incidence of fractures (any grade 0.1% versus [vs.] 0.2%; p=1) (1). However, in patients receiving zoledronic acid, no statistically significant decreases in BMD from baseline after 12, 36, and 60 months were observed in the trochanter and lumbar spine (2). Conversely, for patients who did not receive zoledronic acid, statistically significant decreases from baseline in BMD were observed in the lumbar spine at 12, 36, and 60 months and in the trochanter at 12 and 36 months (2).

For survival-based outcomes, there was no statistically significant difference in OS (98.2% vs. 97.1%, respectively; hazard ratio [HR], 0.60; p=0.11) after a median follow-up of 47.8 months (1). The authors reported a significant difference in disease-free survival (94.0% vs. 90.8%; HR, 0.64; p=0.01) and recurrence-free survival (94.0% vs. 90.9%; HR, 0.65; p=0.01) in favour of zoledronic acid (1). DFS was defined as the time from randomization to local recurrence, contralateral carcinoma, distant metastasis, secondary carcinoma, and/or death and recurrence-free survival as the time from randomization to local relapse, contralateral carcinoma, distant metastasis, and/or secondary carcinoma.

FUTURE RESEARCH

Two ongoing trials were identified (Appendix 2).

RELATED PROGRAM IN EVIDENCE-BASED CARE GUIDELINES**Evidence-based Series**

- EBS #1-9: *Adjuvant Ovarian Ablation in the Treatment of Women with Early Stage Invasive Breast Cancer* [In Development].

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Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775

REFERENCES—SUMMARY

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2. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, Kainberger F, Kassmann H, Piswanger-Solkner JC, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. *Lancet Oncol.* 2008;9(9):840-9.

FULL REPORT

QUESTIONS

1. Does the use of adjuvant zoledronic acid in combination with adjuvant endocrine therapy in premenopausal women with early-stage hormone-receptor-positive breast cancer result in improved outcomes? Outcomes of interest include overall survival (OS), disease-free survival (DFS), recurrence rate, fragility fractures, and adverse events.
2. Which subgroups of patients benefit the most from adjuvant zoledronic acid?
3. What is the optimal dose and schedule of adjuvant zoledronic acid?

INTRODUCTION

Premenopausal women with early-stage hormone-receptor-positive breast cancer commonly receive adjuvant endocrine therapy in the form of either tamoxifen or ovarian suppression/ablation, or both. While the data supporting the use of tamoxifen is well established, the addition of ovarian suppression is more controversial. Indeed the latest data from the Zoladex in Premenopausal Patients (ZIPP) trial did not show a statistically significant benefit in either DFS or OS with the addition of goserelin to tamoxifen (1). In that trial, 2710 patients were randomized to one of no hormonal therapy, tamoxifen alone, goserelin alone, or goserelin plus tamoxifen. OS and DFS were both significantly improved with the use of tamoxifen, goserelin, or both in combination compared to control (1). However, when the authors examined for any interaction between goserelin and tamoxifen, the use of both agents in combination did not demonstrate significant differences in OS or DFS compared to either agent alone. Furthermore, most premenopausal women are treated with cytotoxic chemotherapy, and the role of ovarian suppression in this context remains unclear (Breast Cancer Disease Site Group Evidence-based Series #1-9: *Adjuvant Ovarian Ablation in the Treatment of Women with Early Stage Invasive Breast Cancer [In Development]*). We are therefore left in the rather complex situation of not knowing what the optimal endocrine strategy is in premenopausal women: the current standard of care in Canada would be tamoxifen for five years for premenopausal women, whether previously treated with chemotherapy or not.

What is known is that all these endocrine manipulations (i.e., tamoxifen or GnRH analogues) in premenopausal women are associated with bone loss and an increased fracture risk. A number of bisphosphonates including; alendronate, risedronate, clodronate, and zoledronic acid have been shown to ameliorate this pattern of bone loss in this setting. In recent years, there has been increasing interest in the use of bisphosphonate (i.e., clodronate, ibandronate, and zoledronic acid) as an adjuvant therapy to reduce the risk of breast cancer recurrence. One study has reported significant benefits in terms of DFS and bone mineral density (BMD), using six-monthly zoledronic acid for three years and is the basis for the current report.

The Ontario Ministry of Health and the Committee to Evaluate Drugs - Cancer Care Ontario subcommittee (CED-CCO) asked the Breast Cancer Disease Site Group (DSG) of the CCO Program in Evidence-based Care (PEBC) to provide advice on the adjuvant use of zoledronic acid in combination with adjuvant endocrine therapy in premenopausal women with hormone-receptor-positive breast cancer.

METHODS

This advice report, produced by the CCO PEBC, is a convenient and up-to-date source of the best available evidence on the adjuvant use of zoledronic acid in combination with adjuvant endocrine therapy in premenopausal women with early-stage breast cancer, developed through a systematic review of the available evidence. Contributing authors

disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

MEDLINE (Ovid) (1950 to November Week 3 [Nov 30], 2009), EMBASE (Ovid) (1980 to Week 47 [Nov 30], 2009), and the Cochrane Library (2009, Issue 4) databases were searched. The search strategies for MEDLINE and EMBASE are shown in Appendix 1. Search strategies in other databases were similar.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO) 2005-2009 and the San Antonio Breast Cancer Symposium (SABCS) 2005-2009 were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>), the National Guidelines Clearinghouse (<http://www.guideline.gov/index.asp>), and the National Institute for Clinical Excellence (<http://www.nice.org.uk/>) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published full report articles or published meeting abstracts involving:

1. Randomized trials that compared the **adjuvant** use of zoledronic acid in combination with adjuvant endocrine therapy to either adjuvant endocrine therapy alone or in combination with placebo.
2. Patients who were premenopausal with early-stage hormone-receptor-positive breast cancer.
3. Systematic reviews, meta-analyses, or clinical practice guidelines on the use of adjuvant zoledronic acid in premenopausal women with early-stage hormone-receptor-positive breast cancer.
4. Publications of randomized trials, systematic reviews, or meta-analyses that reported data on one or more of the following outcomes: OS, DFS, recurrence rate, or adverse events.

Exclusion Criteria

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types.
2. Articles published in a language other than English, because of financial considerations for translation.

Synthesizing the Evidence

A meta-analysis of trial results was not conducted as only one trial was identified.

RESULTS

Figure 1 details the results of the literature search. Three full publications (2-4) and two abstracts (5,6) of one randomized trial were identified.

Trial and Patient Characteristics

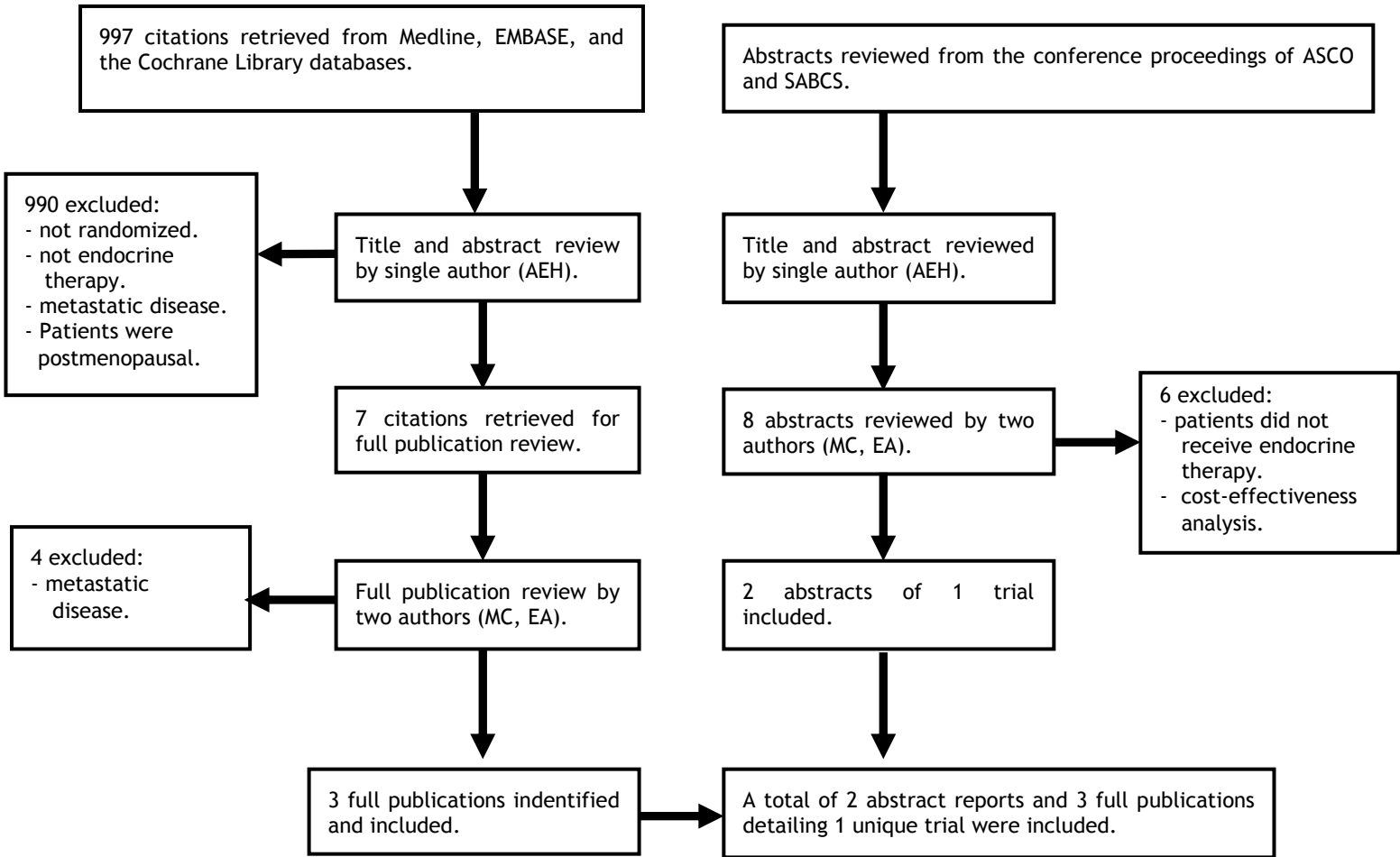
Gnant et al (2) reported the results of the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) that randomized patients, using a two-by-two factorial design, to either goserelin/tamoxifen or goserelin/anastrozole with or without zoledronic acid. Trial and patient characteristics can be found in Table 1. The four arms were balanced for a number of demographic and baseline disease characteristics (2). In particular, there was no adjuvant chemotherapy use and minimal neoadjuvant chemotherapy use (5.4%) in this study.

Table 1. Patient and intervention details for RCTs of zoledronic acid in breast cancer.

Author, year (ref)	Patient characteristics	Treatment	Differences between treatment groups at baseline
Gnant, 2009 (2)	Premenopausal women who had primary surgery who stage I or II estrogen or progesterone-receptor-positive breast cancer with <10 positive lymph nodes.	goserelin 3.6 mg sc q28d + tamoxifen 20 mg/d po; for 3y total	Arms balanced
		goserelin 3.6 mg sc q28d + tamoxifen 20 mg/d po + zoledronic acid 4 mg q6mo; for 3y total	
		goserelin 3.6 mg sc q28d + anastrozole 1 mg/d po; for 3y total	
		goserelin 3.6 mg sc q28d + anastrozole 1 mg/d po + zoledronic acid 4 mg q6mo; for 3y total	

Notes: d=day(s); mo=months; po=orally; q=every; ref=reference; sc=subcutaneous; y=years.

Figure 1. Selection of studies investigating adjuvant zoledronic acid in early-stage breast cancer from the search results of MEDLINE, EMBASE, and the Cochrane Library databases, and the conference proceedings of ASCO and SABCS.



Trial Quality

Quality characteristics of the randomized trial can be found in Table 2. The primary outcome was DFS, which was defined as the time from randomization to local recurrence, contralateral carcinoma, distant metastasis, secondary carcinoma, and/or death (2). Secondary outcomes included OS, recurrence-free survival (RFS), and survival free of bone metastasis. The authors used an appropriate randomization method and concealed treatment allocation. The final analysis was based on the intent-to-treat principle, and the trial was not terminated early. The reported sample size requirement was met. No patients were lost to follow-up.

Table 2. Quality characteristics of identified RCT.

Author, year (ref)	Primary outcome	Required sample size	Secondary outcomes	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Losses to follow-up	Ethical Approval
Gnant, 2009 (2)	DFS	1,800 pts req'd to observe 124 events to reveal a HR of 1.8 between trtmt arms with a two-sided alpha of 0.05 and power of 90%.	OS, RFS, survival free of bone metastasis	Adaptative randomization method with a central call-in centre	Yes	No	Yes	Yes	No	0	Yes

Notes: DFS=disease-free survival; HR=hazard ratio; ITT=intent-to-treat; NR=nor reported; OS=overall survival; pts=patients; ref=reference; RFS=recurrence-free survival; req'd=required; trtmt=treatment.

Outcomes

Bone Mineral Density

A BMD substudy of the ABCSG-12 trial was reported separately by Gnant et al (3-5). The most recent publication (3) reported that 404 patients from the ABCSG-12 trial participated in the substudy. Of those patients, 205 received zoledronic acid in combination with endocrine therapy, while 199 patients received endocrine therapy alone. BMD was assessed in the lumbar spine and trochanter using dual energy X-ray absorptiometry at baseline (three months prior to randomization to 1.5 months after start of treatment) and at six, 12, 36, and 60 months. Standardization of measurements was made possible by regular and standardized calibration of machines at all institutions. With 90 patients per arm, the substudy was designed to detect a decrease in BMD of 0.4% per life year in the two treatment arms not receiving zoledronic acid and an increase of 0.3% per life year in the two treatment arms receiving zoledronic acid, with 80% power and alpha of 0.05.

For patients receiving zoledronic acid, the authors reported no statistically significant difference in BMD at 12, 36, or 60 months in the trochanter (+0.8%, +0.8%, and +3.9%, respectively) and at 12 and 36 months in the lumbar spine (+1.5% and +0.4%) (3). At 60 months, the authors reported a statistically significant increase over baseline in lumbar spine BMD (+4.0%; $p=0.022$). For patients not receiving zoledronic acid, the authors reported statistically significant decreases compared to baseline in BMD at 12, 36, and 60 months in the lumbar spine (-7.4% [$p<0.0001$], -11.3%; $p<0.0001$ and -6.3%; $p=0.001$, respectively) and at 12 and 36 months in the trochanter (-4.1%; $p=0.010$ and -7.3%; $p<0.0001$) (3). At 60 months in the trochanter, no statistically significant decrease in BMD was reported (-4.1%; $p=0.058$) compared to baseline.

No significant differences in both any grade (0.1% vs. 0.2%; $p=1$) and grade 3-4 (1.2% vs. 1.1%; $p=0.83$) fracture were reported for zoledronic acid compared to no zoledronic acid (2).

Survival Outcomes

Data for survival-based outcomes can be found in Table 3.

Table 3. Efficacy outcomes for RCTs of zoledronic acid in early-stage breast cancer.

Author, year (ref)	Treatment	N	DFS	OS	RFS	Follow-up (months)
Gnant, 2009 (2)	Zoledronic acid	899	94.0%	98.2%	94.0%	47.8
	No zoledronic acid	904	90.8%	97.1%	90.9%	
			HR=0.64	HR=0.60	HR=0.65	
			95% CI 0.46-0.91;	95% CI 0.32-1.11;	95% CI 0.46-0.92;	
			$p=0.01$	$p=0.11$	$p=0.01$	
	Anastrozole/goserelin	903	92.0%	97.0%	92.0%	
			92.8%	98.3%	92.9%	
	Tamoxifen/goserelin	900	HR=1.10	HR=1.80	HR=1.11	
			95% CI 0.78-1.53;	95% CI 0.95-3.38;	95% CI 0.80-1.56;	
			$p=0.59$	$p=0.07$	$p=0.53$	

Notes: CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; N=number randomized; NR=not reported; OS=overall survival; RCT=randomized controlled trial; ref=reference; RFS=recurrence-free survival.

The authors reported a significant difference in DFS (hazard ratio [HR] 0.64; $p=0.01$) and RFS (HR 0.65; $p=0.01$) for zoledronic acid compared to no zoledronic acid after a median follow-up of 47.8 months (2). No significance difference in OS existed for zoledronic acid compared to no zoledronic acid (HR 0.60; $p=0.11$) arms. The authors reported no statistically significant differences in OS, DFS, or RFS for anastrozole and goserelin compared to tamoxifen and goserelin after a median follow-up of 47.8 months (Table 3).

It is possible that the benefit seen from zoledronic acid may be confounded by the endocrine therapy used. Of the 137 DFS events that occurred, 72 occurred in patients treated with anastrozole, and the remaining 65 occurred in those treated with tamoxifen. Although this was not statistically significant, it questions the role of anastrozole in this setting. There is a biological rationale for the view that the particularly marked bone loss in patients who received a combination of goserelin and anastrozole may have provided a more fertile microenvironment for the formation of the metastatic niche and that the positive effects of zoledronic acid were driven by the inhibition of this bone loss.

Toxicity

Gnant et al (2) reported that treatment with zoledronic acid resulted in higher incidences of any grade bone pain, arthralgia, fever, peripheral nerve disease, tachycardia, skin disease, cognitive disorder, cutaneous reaction, and nausea and vomiting compared to no zoledronic acid (Table 4). The authors reported that there were no significant differences in serious (grade 3 or 4) adverse events for zoledronic acid compared to none. No cases of osteonecrosis of the jaw were reported in either any of the study arms.

Table 4. Adverse events in RCTs of zoledronic acid in early-stage breast cancer.

Author, year (ref)	Treatment	N	Arthralgia (%)	Peripheral nerve disease (%)	Tachycardia (%)	Skin disease (%)	Cognitive disorder (%)	Fever (%)	Nausea/vomiting (%)	Cutaneous reaction (%)	Bone pain (%)
Gnant, 2009 (2)	Zoledronic acid	899	23.9	5.7	2.1	6.5	1.4	8.9	8.6	2.2	35.3
	No zoledronic acid	904	18.2 p=0.003	3.4 p=0.02	0.8 p=0.02	4.3 p=0.05	0.3 p=0.01	2.2 p<0.001	6.1 p=0.05	4.1 p=0.03	24.7 p<0.001

Notes: N=number randomized; RCT=randomized controlled trial; ref=reference.

DISCUSSION

Only one trial of adjuvant zoledronic acid in combination with adjuvant endocrine therapy in premenopausal women with early-stage breast cancer was identified (2-6). The authors treated all patients with goserelin/tamoxifen or goserelin/anastrozole with or without zoledronic acid. Patients received all treatment for a total of three years. The trial demonstrated statistically significant differences in the primary outcome, DFS, as well as RFS, (Table 3) for zoledronic acid compared to no zoledronic acid. No statistically significant difference in OS for zoledronic acid compared to none was detected after a median follow-up of 47.8 months. In addition, no statistically significant differences in OS, DFS, or RFS were detected for anastrozole and goserelin compared to tamoxifen and goserelin (Table 3). While the trial was not powered to detect a difference in OS, the generalizability of the trial results to the premenopausal women with early-stage hormone-receptor-positive breast cancer is questionable for a number of reasons (2). First, the trial treated patients for a total of three years, while standard treatment is generally considered to be five years of tamoxifen. Second, ongoing studies are evaluating the role of tamoxifen and aromatase inhibitors together with ovarian suppression in similar patient populations. Though of note, the Suppression of Ovarian Function (SOFT) and Tamoxifen and Exemestane (TEXT) trials will contain many more patients treated with chemotherapy than the ABCSG-12 study.

The ABCSG-12 trial also reported no statistically significant difference in BMD in the lumbar spine and the trochanter compared to baseline for patients who received zoledronic acid, whereas a significant decrease in BMD compared to baseline was reported for patients who did not receive zoledronic acid. However, the authors also reported no statistically significant differences in any grade or grade 3-4 fractures for patients who received zoledronic acid compared to those who did not.

Given the lack of OS difference and the lack of difference in risk of fracture, there is insufficient evidence to support the routine use of zoledronic acid in combination with adjuvant endocrine therapy (as defined in the ABCSG-12 trial) in premenopausal women with early-stage hormone-receptor-positive breast cancer. Future trials should be powered to detect differences in OS and use a standard duration of treatment. In addition, longer follow-up would help to determine if the risk of fracture would remain the same many years after the completion of adjuvant treatment.

CONCLUSIONS

The following statements reflect the opinions of the authors of this special advice report:

The adjuvant use of zoledronic acid in combination with adjuvant endocrine therapy and gonadal suppression in premenopausal women as treatment for early-stage breast

cancer appears to be associated with an improved DFS, based on the results of the ABCSG-12 trial. However, the combination of ovarian suppression with either tamoxifen or anastrozole and the provision of only three years of systemic therapy would not be considered a standard of care.

The use of zoledronic acid in combination with adjuvant endocrine therapy and gonadal suppression combined with either tamoxifen or anastrozole in premenopausal women with early-stage breast cancer may be a treatment option to reduce cancer therapy-induced bone loss, based on the results of the ABCSG-12 trial; however, such a strategy does not appear to reduce clinical fracture incidence. Similar findings have been demonstrated with other bisphosphonates.

ONGOING TRIALS

Searches were made of the National Cancer Institute clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the National Institutes of Health Clinical Trials database (<http://clinicaltrials.gov/>) for reports of new or ongoing randomized trials investigating the adjuvant use of zoledronic acid combination with adjuvant endocrine therapy in premenopausal women with early-stage hormone-receptor-positive breast cancer. Appendix 2 provides details of the identified ongoing trials.

CONFLICT OF INTEREST

The authors of this special advice report disclosed potential conflicts of interest relating to the topic of this special advice report. One author (MC) declared honoraria and research support from Novartis. Another author (MT) declared an unrestricted educational grant from Novartis. The remaining authors (EA, AEH) reported no conflicts of interest.

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Appendix 1. Literature search strategies.

Ovid MEDLINE

1. diphosphonates/
2. bone density conservation agents/
3. organophosphorus compounds/
4. zoledronate.mp.
5. zometa.mp.
6. zomera.mp.
7. aclasta.mp.
8. reclast.mp.
9. bisphosphonate:.mp.
10. diphosphonate:.mp.
11. or/1-10
12. exp breast neoplasms/
13. breast cancer:.mp.
14. 12 or 13
15. 11 and 14
16. meta-analysis as topic/
17. meta analysis.pt.
18. meta analy\$.tw.
19. metaanaly\$.tw.
20. (systematic adj (review\$1 or overview\$1)).tw.
21. or 16-20
22. Cochrane.ab.
23. embase.ab.
24. (cinahl or cinhal).ab.
25. science citation index.ab.
26. bids.ab.
27. cancerlit.ab.
28. or/22-27
29. reference list\$.ab.
30. bibliography\$.ab.
31. hand-search\$.ab.
32. relevant journals.ab.
33. manual search\$.ab.
34. or/29-33
35. selection criteria.ab.
36. data extraction.ab.
37. 35 or 36
38. review.pt.
39. review literature as topic/
40. 38 or 39
41. 37 and 40
42. comment.pt.
43. letter.pt.
44. editorial.pt.
45. or/42-44
46. 21 or 28 or 34 or 41
47. 46 not 45
48. randomized controlled trials as topic/

49. randomized controlled trial.pt.
50. random allocation/
51. double blind method/
52. single blind method/
53. clinical trials, phase III as topic/
54. clinical trial, phase III.pt.
55. clinical trials, phase II as topic/
56. clinical trial, phase II.pt.
57. (clinic\$ adj trial\$1).tw.
58. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
59. placebos/
60. placebo\$.tw.
61. (allocated adj2 random\$).tw.
62. random allocation.tw.
63. randomly allocated.tw.
64. or/48-63
65. case report.tw.
66. letter.pt.
67. historical article.pt.
68. or/65-67
69. 64 not 68
70. 47 or 69
71. practice guideline/
72. practice guideline\$.mp.
73. 71 or 72
74. 70 or 73
75. 15 and 74
76. limit 75 to (English language and humans)

EMBASE

1. bisphosphonic acid derivative/
2. organophosphorus compound/
3. bisphosphonate:.mp.
4. diphosphonate:.mp.
5. zoledronate.mp.
6. zoledronic acid.mp.
7. zometa.mp.
8. zomera.mp.
9. aclasta.mp.
10. reclast.mp.
11. or/1-10
12. exp breast cancer/
13. exp breast tumor/
14. breast cancer:.mp.
15. or/12-14
16. 11 and 15
17. exp meta-analysis/
18. ((meta adj analy\$) or metaanaly\$).tw.
19. (systematic adj (review\$1 or overview\$1)).tw.
20. or/17-19

21. cancerlit.ab.
22. Cochrane.ab.
23. embase.ab.
24. (cinahl or cinhal).ab.
25. science citation index.ab.
26. bids.ab.
27. or/21-26
28. reference list\$.ab.
29. bibliography\$.ab.
30. hand-search\$.ab.
31. manual search\$.ab.
32. relevant journals.ab.
33. or/28-32
34. data extraction.ab.
35. selection criteria.ab.
36. 34 or 35
37. review.pt.
38. 36 and 37
39. letter.pt.
40. editorial.pt.
41. 39 or 40
42. 20 or 27 or 33 or 38
43. 42 not 41
44. randomized controlled trial/
45. randomization/
46. single blind procedure/
47. double blind procedure/
48. placebo/
49. randomi?ed control\$ trial\$.tw.
50. rct.tw.
51. random allocation.tw.
52. randomly allocated.tw.
53. allocated randomly.tw.
54. (allocated adj2 random\$).tw.
55. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
56. placebo\$.tw.
57. or/44-56
58. case study/
59. case report.tw.
60. abstract report/
61. letter/
62. or/58-61
63. 57 not 62
64. exp practice guideline/
65. practice guideline\$.tw.
66. 64 or 65
67. 43 or 63 or 66
68. 16 and 67
69. limit 68 to (human and English language)

Appendix 2. Ongoing trials.**Chemotherapy and/or hormone therapy with or without zoledronate in treating women with stage II or stage III breast cancer.**

Patients: receiving or scheduled to receive chemotherapy and/or endocrine therapy. For patients receiving adjuvant therapy: undergone complete primary resection. For patients receiving neoadjuvant therapy: scheduled to receive definitive surgery or radical radiotherapy with curative intent.

Protocol ID:	CDR0000335111, SHEFF-AZURE, EU-20315, ISRCTN79831382, BIG-1-04
Last date modified:	February 6, 2009
Trial type:	Open-label randomized trial with active control
Accrual:	3,330 patients
Primary outcome:	Disease-free survival
Sponsors:	University of Sheffield
Status:	Ongoing, not recruiting patients

Zoledronate, clodronate, or ibandronate in treating women who have undergone surgery for stage I, stage II, or stage III breast cancer.

Patients: Hormone-receptor status not specified; menopausal status not specified.

Protocol ID:	CDR0000437061, SWOG-S0307, NCCTG-SWOG-S0307, ECOG-SWOG-S0307, NSABP-SWOG-S0307, CALGB-SWOG-S0307, CAN-NCIC-SWOG-S0307
Last date modified:	January 13, 2010
Trial type:	Randomized, active control
Accrual:	5,400 patients
Primary outcome:	Disease-free survival, overall survival, histologically-confirmed disease recurrence, sites of first disease recurrence, Zubrod performance status
Sponsors/ collaborators:	Southwest Oncology Group (SWOG); National Cancer Institute (NCI); North Central Cancer Treatment Group (NCCTG); Eastern Cooperative Oncology (ECOG); National Surgical Adjuvant Breast and Bowel Project (NSABP); Cancer and Leukemia Group B (CALGB); National Cancer Institute of Canada (NCIC) Clinical Trials Group
Status:	Recruiting