Bisphosphonates and Breast Cancer

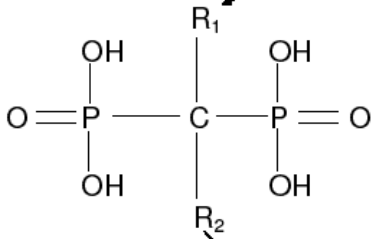
Bisphosphonates

- Analogues of pyrophosphate
- Carbon substitution makes them resistant to endogenous phosphatases in circulation
- Potent inhibitors of osteoclast growth, maturation and function
- Poorly absorbed via GI tract
- Structure function/potency relationship

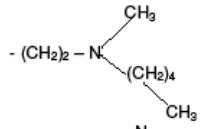
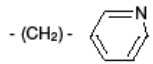
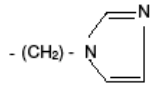
Structure and Potency of Clinically useful Bisphophonates

Figure 1. Bisphosphonate structure and relative potencies

When R_1 = OH, tridentate binding facilitates calcium binding

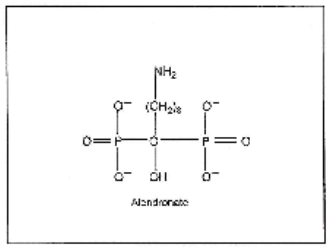


The complexity of the R_2 side chain is directly related to potency

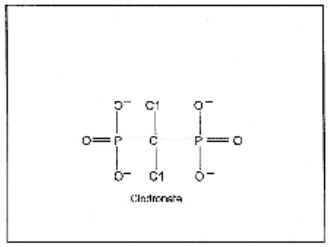
Compound	R_2	Relative Potency
Etidronate	$-CH_3$	1
Clodronate	- Cl	10
Pamidronate	$-(CH_2)_2-NH_2$	100
Alendronate	$-(CH_2)_3-NH_2$	100
Ibandronate		1,000
Risendronate		1,000
Zoledronate		10,000

Structure and Potency of Clinically useful Bisphophonates

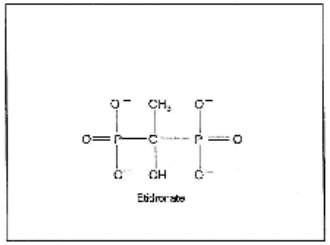
(Fig 1)



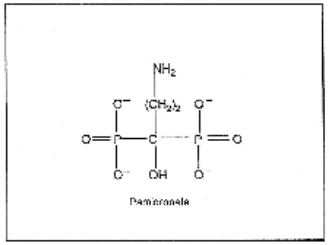
Alendronate



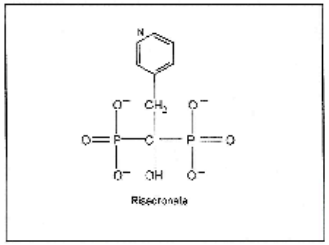
Clodronate



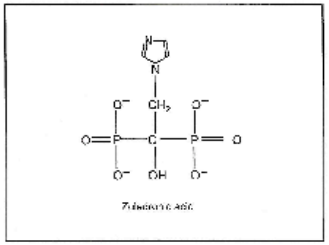
Etidronate



Pamidronate



Risedronate



Zoledronic acid

Bisphosphonate Mechanisms of Action

- Bind to hydoxyapatite crystals – inhibit breakdown
- Preferentially incorporated into active bone remodeling sites
- Promote osteoclast apoptosis – inhibit mevalonic acid pathway

Drake MT et al Mayo Clin Proc 2008;83:1032-1045

Metastatic Breast Cancer

- Pamidronate
- Zoledronic acid
- Ibandronate
- Clodronate

Prospective randomized trials of bisphosphonates in bone metastasis from breast cancer

Author	Date	# Pts	Placebo control	Agent/route	Fracture Risk	Radiation	Surgery	HCM	Pain	Survival
Elomaa	1987	34	Yes	Clodronate po	↓	NR	NR	↓	↓	Better
Paterson	1993	173	Yes	Clodronate po	↓	↓		↓	↓	No diff
van Holten-Verzantvoort	1987	131	No	Pamidronate po	No diff	↓	No diff	↓	↓	No diff
Conte	1996	161	No	Pamidronate IV	No diff	No diff	No diff	↓	↓	No diff
Hortobagyi*	1996	382	Yes	Pamidronate IV	↓	↓	↓	↓	↓	No diff
Theriault*	1996	372	Yes	Pamidronate IV	↓	↓	No diff	↓	↓	No diff
Hortobagyi•	1998	382	Yes	Pamidronate IV	↓	↓	↓	↓	↓	No diff
Theriault•	1998	372	Yes	Pamidronate IV	↓	↓	No diff	↓	↓	No diff

*12 month analysis
•24 month analysis

↓ - Decreased
NR – Not reported
No Diff – No difference

Prospective randomized trials of bisphosphonates in bone metastasis from breast cancer
References

Elomaa I, Blomqvist C, Porkka L, et al. Bone 1987;8:S53

Paterson AHG, Popwles TJ, Kanis JA et al. J Clin Oncol 1993;11:59

van Holten-Verzantvoort AT, Bijvoet OLM, Hermans J et al. Lancet 1987;2:983

Hortobagyi GN, Theriault RL, Porter L et al. N Engl J Med 1996;335:1785

Theriault RL, Lipton A, Leff R et al. Proc Am Soc Clin Oncol 1996;15:122 (abst)

Hortobagyi GN, Theriault RL, Lipton RL et al. J Clin Oncol 1999;17:846

Conte PF, Latreille J, Mauriac L et al. J Clin Oncol 1996;14:2552

Metastatic Breast Cancer

- Zoledronic acid vs pamidronate
- Randomized, double blind, trial
- 1648 patients
- Zoledronic acid 4 mg iv q 3-4 weeks OR
- Pamidronate 90 mg iv q 3-4 weeks
- Duration of study drug 24 months

Rosen et al Cancer 2003;98:1735-1744

Metastatic Breast Cancer
Zoledronic Acid vs. Pamidronate

Combination of 2 randomized controlled trials 1130 patients – breast cancer – osteolytic bone mets

Zoledronic acid 4mg IV q 3-4 weeks OR

Pamidronate 90 mg IV q 3-4 weeks

12 month observation

Results:

Proportion with skeletal related events (SRE)

Zoledronic Acid	**Pamidronate**	
43%	45%	overall
48%	58%	lytic disease
Time to first SRE (days)		
310	174	

Rosen LS et al, Cancer 2004;100:36-43

Metastatic Breast Cancer
Zoledronic acid vs. Pamidronate – Long Term Efficacy

	Zoledronic Acid	Pamidronate	p value
SRE (%)	46%	49	NS
SRE (XRT)	19%	24%	0.037
Time to 1st SRE (days)	376	356	NS
Time to 1st SRE (days) br ca endocrine	415	370	0.047
SMR	.9	1.49	0.125

NCCN Guideline Recommendation
BINV – 16 footnote "X"

- Pamidronate or zoledronic acid (with calcium 1200-1500mg and vitamin D 400-800 IU daily supplement) should be given (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis present, expected survival $\geq$ 3 months and creatinine $\leq$ 3.0 mg/dL.

Clinical Endpoints

- Decrease fracture risk
- Decrease need for radiation to bone
- Decrease need for surgery for bone
- Improve pain

Bisphosphonates and Metastases

- Established role in metastatic bone disease
  - Data sources
    - Randomized, placebo controlled trials
    - Randomized controlled trials
    - Meta analyses
    - Cochrane reviews

Patient Supplements

- Calcium 1200 – 1500 mg po daily
- Vitamin D 400 – 800 IU po daily
- Pre-administration assessment
  - Serum creatinine (adjust bisphosphonate per FDA black box)
  - **Dental evaluation and treatment as needed**

Weitzman R, Sauter N, Eriksen EF, Tarassoff PG, Lacerna LV, Dias R et al. Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients--May 2006. *Crit Rev.Oncol.Hematol.* 2007;62:148-52.

Guidelines Revision Recommended

- Bisphosphonate for bone metastasis. Pamidronate 90mg IV over not less than 2 hours monthly (FDA approved) ***OR*** Zoledronic acid 4mg IV over not less than 15 minutes monthly (FDA approved).
- Ibandronate 6mg IV over 1-2 hours monthly (not FDA approved)

Tripathy D, Body JJ, Bergstrom B. Review of ibandronate in the treatment of metastatic bone disease: experience from phase III trials. *Clin.Ther.* 2004;26:1947-59.

Pecherstorfer M, Rivkin S, Body JJ, Diel I, Bergstrom B. Long-term safety of intravenous ibandronic acid for up to 4 years in metastatic breast cancer: an open-label trial. *Clin.Drug Investig.* 2006;26:315-22.

Bisphosphonates Cancer Treatment Induced Bone Loss (CTIBL)

- NCCN Guideline – None
- Background
  - Chemotherapy and ovarian ablation result in bone loss
  - Presumed mechanism hypoestrogenism
  - Aromatase inhibitors result in bone less and increased fracture risk

CTIBL – Studies with Bisphosphonates

Risedronate				
Study	**# Pt**	**End Point**	**Agents**	**Results**
DBRCT	53	BMD-LS, hip	Risedronate/ placebo 30mg daily x 2 weeks, 10 weeks rest x 8 cycles	Improved BMD LS/hip with risedronate
DBRCT	87	BMD LS/hip	Risedronate 35 mg weekly/or placebo	Improved BMD LS/hip
DBRCT	216	BMD LS	Risedronate 35 mg/weekly or placebo	No difference in BMD LS at 12 mos
Ibandronate				
DBRCT	131	BMD	Ibandronate 150mg/placebo	Improved BMD LS/hip

CTIBL – Studies with Bisphosphonates References

Delmas Pd, Balena R, Confravreux E, Hardouin C, Hardy P, Bremond A. Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double-blind, placebo-controlled study. *J Clin Oncol* 1997;15:955-62.

Greenspan SL, Bhattacharya RK, Sereika SM, Brufsky A, Vogel VG. Prevention of bone loss in survivors of breast cancer: A randomized, double-blind, placebo-controlled clinical trial. *J.Clin.Endocrinol.Metab* 2007;92:131-6.

Sloan, J. A., Thomas, S. P, Chottiner, C. L., Loprinzi, C. L., Atherton, P. J., Carlson, M. D., Salim, M, and Perez, E. A. A phase III randomized, placebo-controlled, double-blind trial of risedronate for prevention of bone loss in premenopausal women undergoing adjuvant chemotherapy for breast cancer (BC). jco 26, 12s. 5-20-2008.

Lester, D, Dodwell, D., Purohit, O. P., gutcher, A, ellis, R, thorpe, j. m., horsman, j. e., brown, r. a., hannon, r. e., and col. Use of monthly oral ibandronate to prevent anastrozole-induced bone loss during adjuvant treatment for breast cancer: Two-year results from ABIRON study. jco 26, 19s. 5-20-2008.

CTIBL – Studies with Bisphosphonates

Pamidronate and Zoledronic Acid				
Type Study	**# Pts**	**Endpoint**	**Agent**	**Result**
DBRCT	40	BMD LS/hip	Pamidronate 60mg IV q 3 months/ placebo	Improved BMD LS/hip
RCT	401	BMD/LS	Zoledronic acid 4mg IV q 6 mos.	Prevented LS bone loss
RCT	602	BMD LS/hip	Zoledronic acid 4mg IV q 6 months x 5 years up front vs. delayed	Up front prevented BMD loss LS/hip
RCT	1065	BMD LS/hip	Zoledronic acid 4mg IV q 6 months x 5 years up front vs. delayed	Up front improved LS/hip BMD
RCT	166	BMD LS	Zoledronic acid 4mg IV q 3 months vs. nil	Improved LS BMD

CTIBL – Studies with Bisphosphonates References

Fuleihan G, Salamoun M, Mourad YA, Chehal A, Salem Z, Mahfoud Z et al. Pamidronate in the prevention of chemotherapy-induced bone loss in premenopausal women with breast cancer: a randomized controlled trial. *J Clin Endocrinol.Metab* 2005;90:3209-14.

Gnant MF, Mlineritsch B, Luschin-Ebengreuth G, Grampp S, Kaessmann H, Schmid M et al. Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. *J.Clin.Oncol.* 2007;25:820-8.

Brufsky A, Harker WG, Beck JT, Carroll R, Tan-Chiu E, Seidler C et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J.Clin.Oncol.* 2007;25:829-36.

Bundred NJ, Campbell ID, Davidson N, DeBoer RH, Eidtmann H, Monnier A et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. *Cancer* 2008;112:1001-10.

Shapiro CL et al. J Clin Oncol, 2008;26:9S Abstract 512

Conclusions

- Bisphosphonates preserve BMD lumbar spine and hip in pre menopausal women with amenorrhea and/or ovarian failure.
- Bisphosphonates preserve BMD lumbar spine and hip in post menopausal women treated with an aromatase inhibitor.
- No data on fracture risk reduction

Recommended Guideline Modification *NOT APPROVED*

- Consider use of bisphosphonate in the adjuvant setting for preservation of BMD
  - Pre-menopausal women treated with gonadotoxic therapy – chemotherapy, ovarian ablation
  - Post - menopausal women treated with aromatase inhibitor

Recommended Guideline Modification *NOT APPROVED*

- Zoledronic acid 4mg IV q3 months for up to 12 months for pre menopausal women receiving gonadotoxic chemotherapy or treated with oophorectomy/ovarian suppression with or without an aromatase inhibitor in the adjuvant setting.
- Zoledronic acid 4mg IV q6 months for up to 5 years beginning with start of aromatase inhibitor adjuvant therapy.

Monitoring of Bone Health

- Monitor BMD at baseline, 12 months and annually
- Calcium 1200 – 1500 mg po daily
- Vitamin D 400 – 800IU daily
- Dental exam and treatment prior to bisphosphonate use
- Monitor serum creatinine per FDA recommendation

Adjuvant Bisphosphonate

- Potential to reduce recurrence and death from breast cancer
- Moot point if bisphosphonate used for BMD preservation.

Oral Clodronate for Primary Breast Cancer

- 1069 patients
- Oral clodronate 1600 mg/day or placebo
- 2 years of therapy – start within 6 months
- Endpoint – bone relapse

Powles T et al. J Clin Oncol 2002; 20:3219-3224

Results
Powles et al.

- During clodronate – significant decrease in bone mets
- Significant reduction in mortality during follow-up (23% reduction)

Powles T et al. J Clin Oncol 2002; 20:3219-3224
Atula S et al. Drug Safety 2003; 26:661-671

Reductions in New Metastases in Breast Cancer with Adjuvant Clodronate

- 302 patients primary breast cancer
- Bone marrow positive by cytokeratin (at least one cell)
- Clodronate 1600 mg daily or nil
- 2 years treatment
- Endpoints – distant mets, survival

Diel IJ et al. N Engl J Med 1998; 339:357

Results
Diel et al.

Distant mets	21 clodronate	42 nil
Deaths	6 clodronate	22 nil
Bone mets	12 clodronate	25 nil
Median follow-up	36 months	

Diel IJ et al. N Engl J Med 1998; 339:357
Diel IJ et al. Cancer 2000;3080-3088

Adjuvant clodronate treatment does not reduce skeletal metastases in node positive breast cancer

- 299 patients – node positive breast cancer
- Clodronate 1600 mg daily or nil
- 3 years of treatment
- 5 years follow-up
- Endpoints – distant mets, survival

Saarto T et al. J Clin Oncol 2001; 19:10-17

Results
Saarto et al.

Bone mets	29 clodronate	24 nil
Non-bone mets	60 clodronate	36 nil
Survival	70%	83%

Saarto T et al. J Clin Oncol 2001; 19:10-17

- Powles
  - Clodronate improved 5 year survival for stage II and III disease 76.7% vs. 69.2%
  - At 10 years ↓ risk of death 23% overall and 26% in stage II and III disease
- Diel
  - Survival advantage at 103 months follow-up
- Saarto
  - Study criticized for imbalance of randomization ER status, PR status
  - ER(-) postmenopausal women treated with tamoxifen

Zoledronic acid in Premenopausal Women Treated with Adjuvant Ovarian Suppression + Tamoxifen or Ovarian Suppression + Aromatase Inhibitor, ± Zoledronic acid 4mg IV q 6 months

- 1801 premenopausal women endocrine responsive breast cancer
- End points
  - Primary DFS
  - Secondary RFS, OS
  - Exploratory bone mets free survival
- Median Follow-up 60 months
  - Results
    - **DFS improved with zoledronic acid (HR=0.64 [0.46-0.91]) p = 0.01**
    - Improved RFS p = 0.10
- Conclusion – zoledronic acid has anti-tumor activity

Gnant, M., Mlineritsch, B., schippinger, W, Luschin-Ebengreuth, G., poestlberger, s, Menzel, C., Jakesz, R., Kubista, E., and Marth, C. Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with endocrine-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12. jco 26(18s), 1006s. 6-20-2008.

Zoledronic acid in post menopausal women with endocrine responsive primary breast cancer treated with adjuvant letrozole

- 1667 patients
- Zoledronic acid 4mg IV q 6 months (up front vs. delayed)
- End point 1° BMD LS at 12 months of study
  - 2° time to recurrence
  - Total hip BMD
  - Changes in bone tumor markers
  - safety
- Results
  - Improved BMD - LS and total hip
  - Fracture rates similar
- Recurrences
  - **7 in upfront group**
  - **17 in delayed group** P=0.0401

Brufsky A, Bundred N, Coleman R, Lambert-Falls R, Mena R, Hadji P et al. Integrated analysis of zoledronic Acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist*. 2008;13:503-14.

NSABP B-34

- Primary breast cancer
- Clodronate vs. placebo
- 3323 subjects
- Closed to accrual March 31, 2004
- Analyses pending

Bone Metastases Prevention

- SWOG – RCT adjuvant bisphosphonate within 12 weeks of surgery (6000 participants)
  - Clodronate 1600mg po daily
  - Zoledronic acid 4mg IV q 4 weeks for 6 months, then q 3 months for 2.5 years
  - Ibandronate 50mg po daily

AZURE Trial

3360 participants

Adjuvant chemotherapy and/or endocrine therapy

Zoledronic acid 4 mg IV vs nil	q 3-4 weeks x 6 doses
	q 3 months x 8 doses
	q 6 months x 5 doses

Recommendation

No guideline additions pending large RCT data