Prevention of bone metastasis: role of adjuvant bisphosphonates

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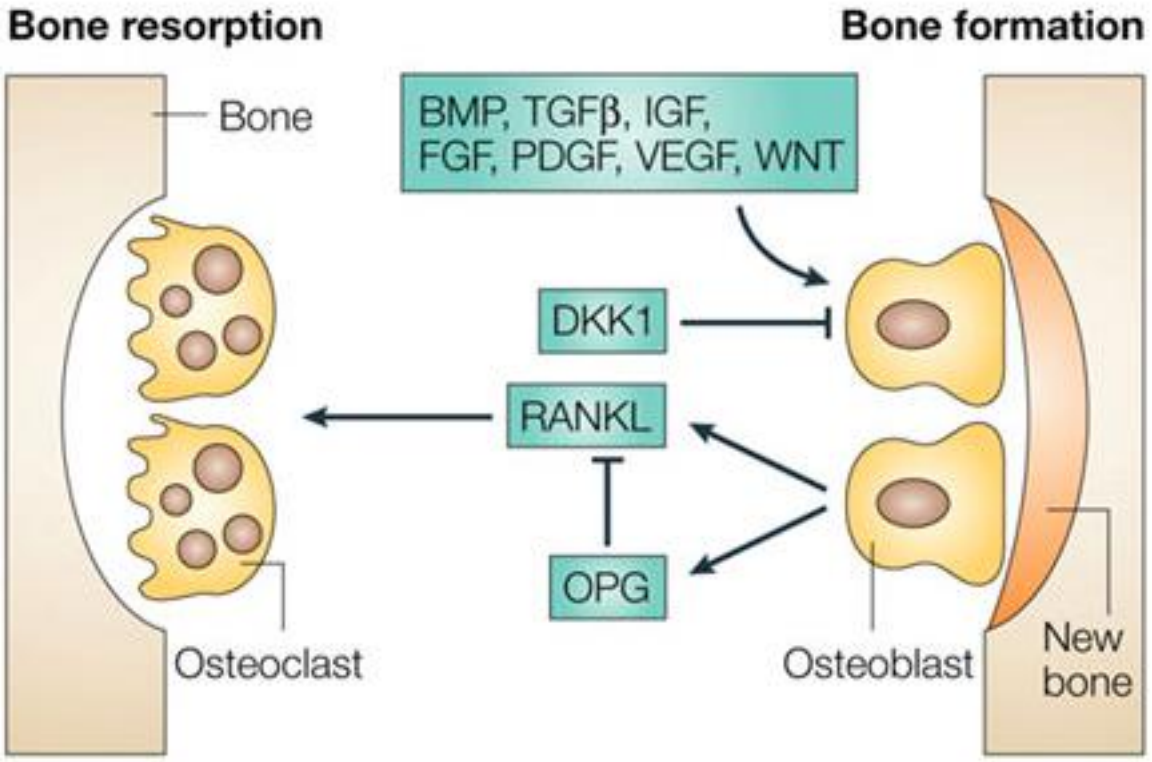
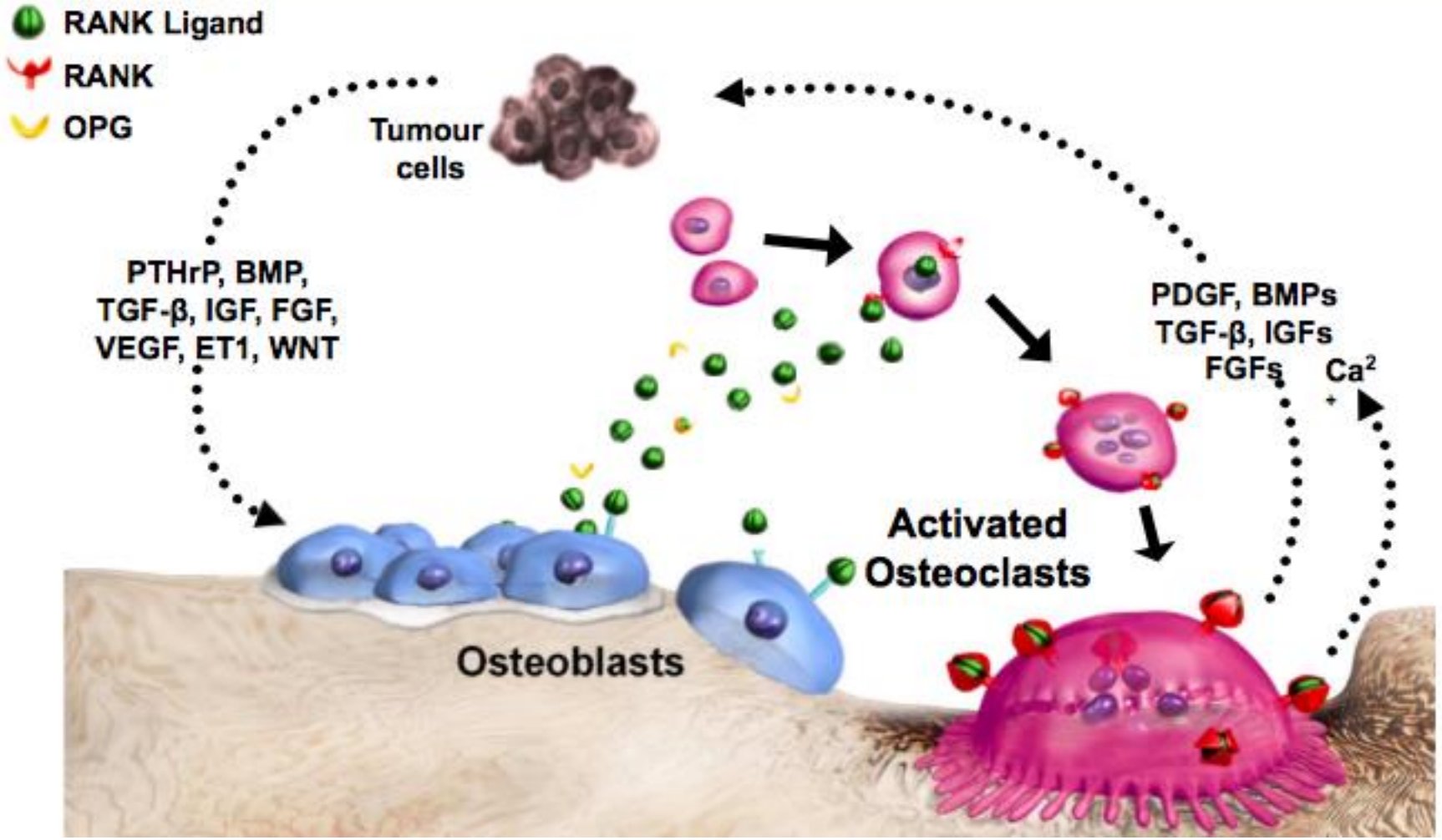
- Introduction
- Mechanism of action and indications
- Role of bisphosphonates in early breast cancer
- Side effects
- Conclusions

Normal bone: fine balance of bone production and resorption

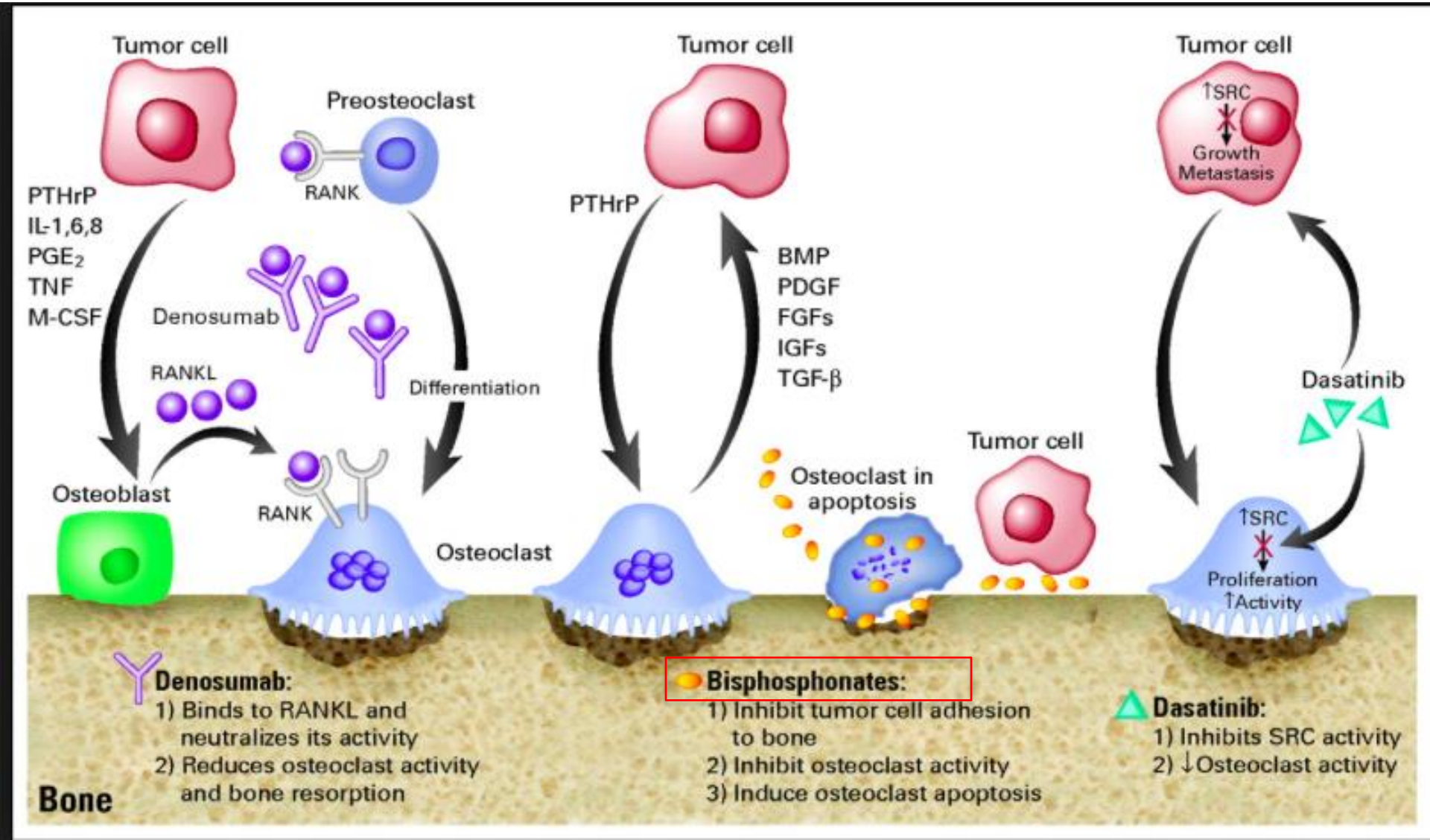


Bone metastasis: tumor-induced bone destruction



NEJM 2002;350:1655

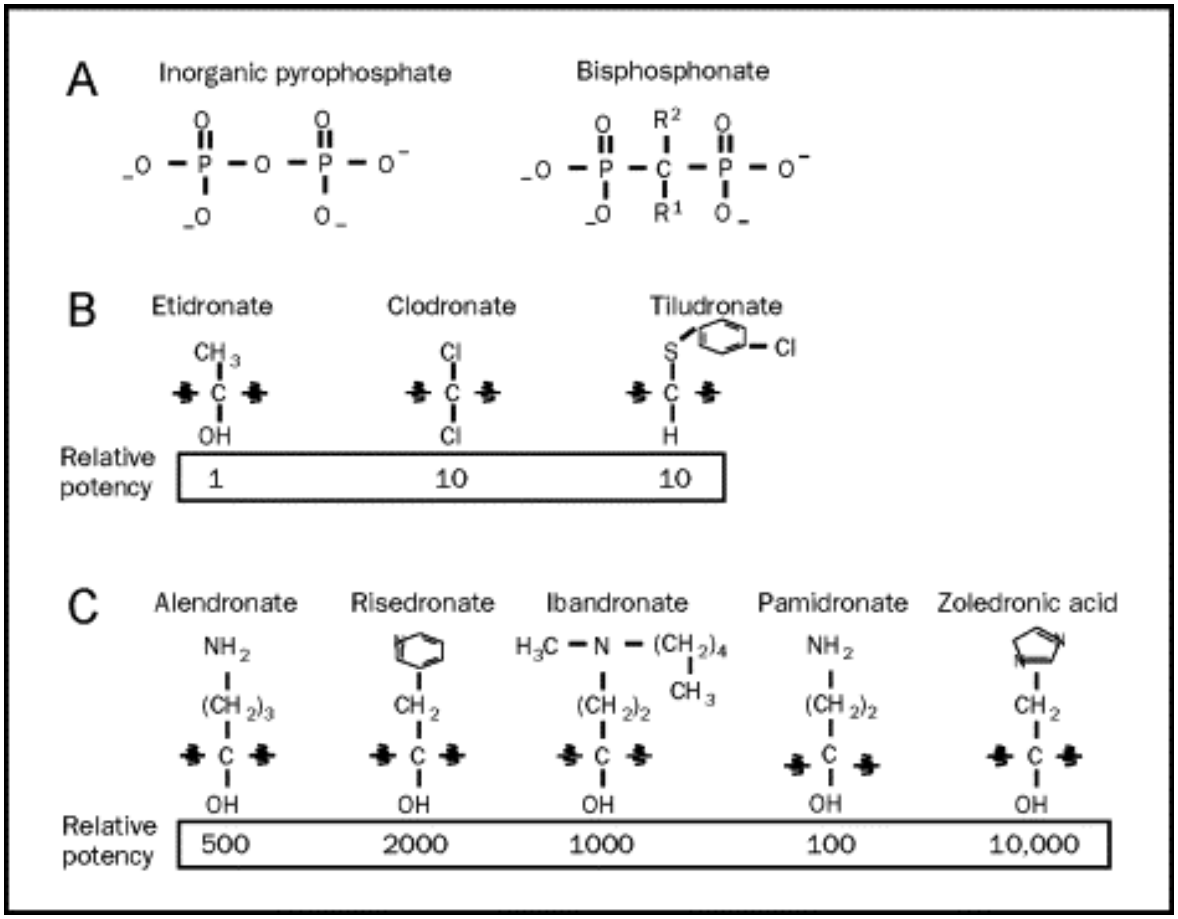
Bone targeted therapies



Bisphosphonates

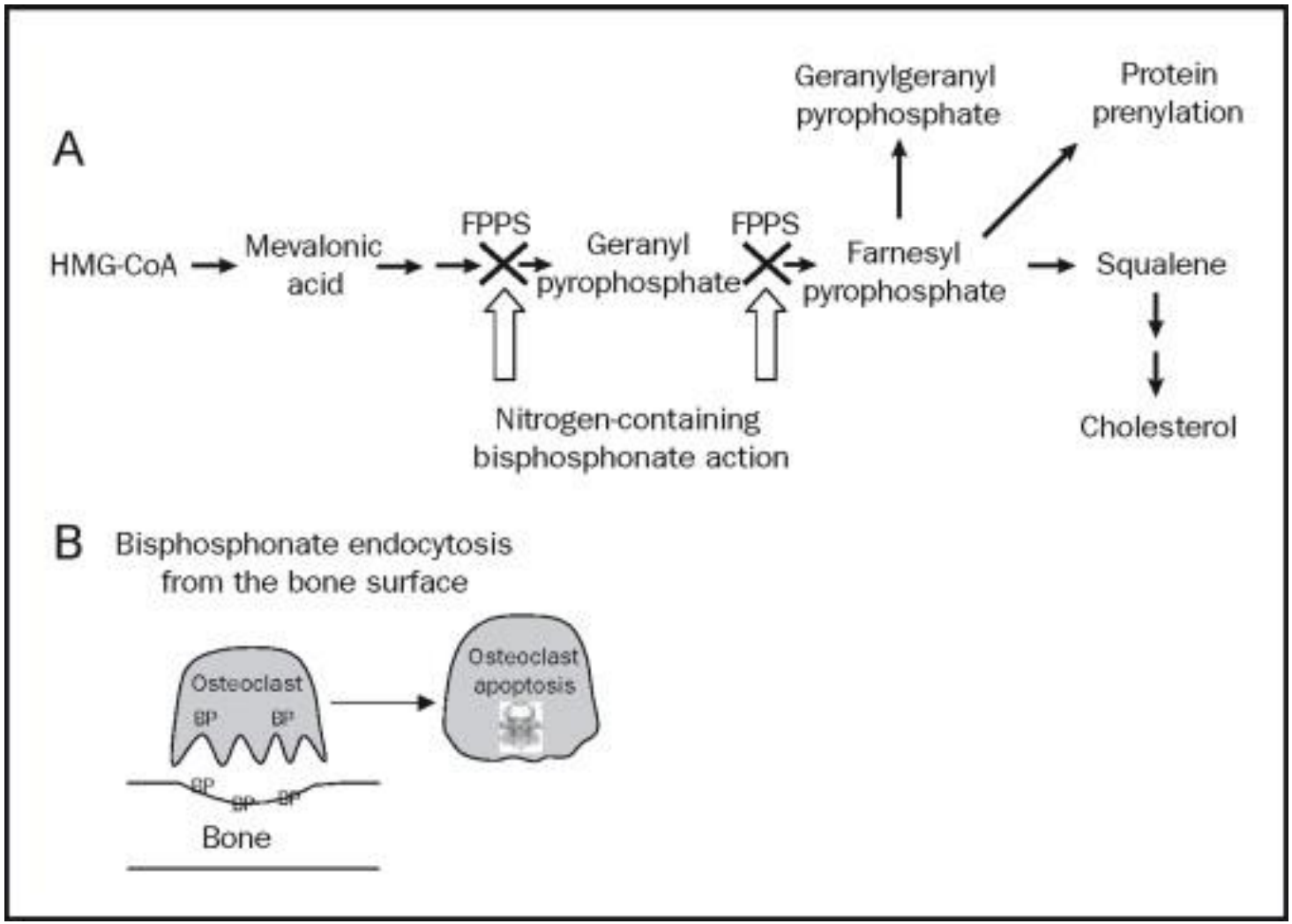
- structural analogs of pyrophosphate that embed into bone inhibiting osteoclast activity and survival
- two classes:
  - (1) nitrogen-containing
  - (2) non–nitrogen-containing

Bisphosphonate structures and approximate relative potencies for osteoclast inhibition



Mayo Clinic Proceedings 2008, 82:1032–1045

Nitrogen-containing bisphosphonates: interrupt the ongoing osteolytic cycle

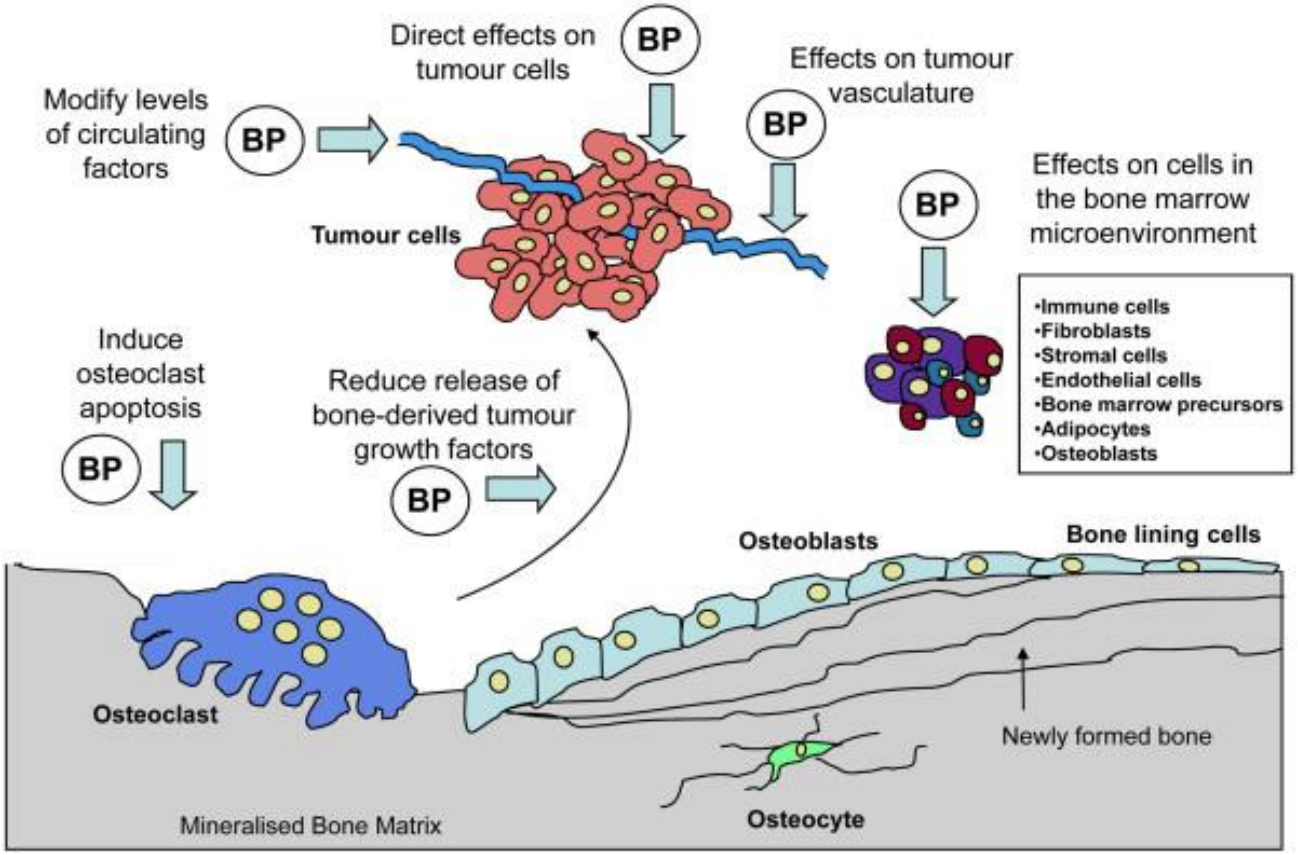


Mayo Clinic Proceedings 2008, 82:1032–1045

Bisphosphonates indications

- role as preventive and therapeutic agents for osteoporosis
- therapy against skeletal-related events among cancer patients with bone metastases, including breast, prostate, and lung malignancies

Bisphosphonates anticancer effect: alter the bone microenvironment



Breast Cancer Research 2010 **12**:214

Bisphosphonates in early breast cancer

- Emerging evidence: benefit of adjuvant bisphosphonates in preventing bone metastasis and improving BC survival
- Several large randomized clinical trials have evaluated the role of aminobisphosphonates in reducing the risk of breast cancer recurrence and death

Oral **clodronate** in Early Breast cancer

Table 3 Major Adjuvant Studies of Oral Clodronate for Early-Stage Breast Cancer

Clinical Trial	N	Study Arms	Follow-up	Outcomes	Summary
Diel 2008[42]	290	Clodronate 1,600 mg/d vs placebo × 2 yr (both pre- and postmenopausal)	8.5 yr	BM: clodronate (37 events) vs placebo (38 events); $P = .77$ VM: clodronate (32 events) vs placebo (33 events); $P = .22$ OS: clodronate (32 events) vs placebo (59 events); $P < .05$	Positive: OS Negative: BM and VM
Saarto 2004[43]	299	Clodronate 1,600 mg/d vs placebo × 3 yr (both pre- and postmenopausal)	10 yr	BM: clodronate (44 events) vs placebo (42 events); $P = .35$ DFS: clodronate (45%) vs placebo (58%); $P < .05$ OS: clodronate (64 events) vs placebo (55 events); $P = .13$	Positive: DFS Negative: BM and OS
Powles 2006[44]	1,069	Clodronate 1,600 mg/d vs placebo × 2 yr (both pre- and postmenopausal)	5 yr	BM: clodronate (51 events) vs placebo (73 events); HR = 0.69; $P < .05$ VM: clodronate (79 events) vs placebo (94 events); HR = 0.84; $P = .24$ OS: clodronate (98 events) vs placebo (129 events); HR = 0.77; $P < .05$	Positive: BM and OS Negative: VM
Paterson 2012[45] **NSABPB-34**	3,323	Clodronate 1,600 mg/d vs placebo × 3 yr (both pre- and postmenopausal)	7.5 yr	BM: clodronate (61 events) vs placebo (80 events); HR = 0.77; 95% CI, 0.55–1.07; $P = .12$ DFS: clodronate (286 events) vs placebo (312 events); HR = 0.91; 95% CI, 0.78–1.07; $P = .27$ OS: clodronate (140 events) vs placebo (167 events); HR = 0.84; 95% CI, 0.67–1.05; $P = .13$	Negative: BM, DFS, and OS

BM = bone metastasis; CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; OS = overall survival; VM = visceral metastasis.

Blanchette PS. Oncology (Williston Park). 2015;29(1):23-30,37

Zoledronic acid in Early Breast Cancer

Table 4 Major Adjuvant Studies of Zoledronic Acid for Early-Stage Breast Cancer

Clinical Trial	N	Study Arms	Follow-up	Outcomes	Summary
Gnant 2011[47] **ABCSG-12**	1,803	Goserelin + endocrine therapy + zoledronic acid vs goserelin + endocrine therapy + placebo × 3 yr (premenopausal)	5 yr	BM: zoledronic acid (21 events) vs placebo (32 events); HR: NR DFS: zoledronic acid (76 events) vs placebo (110 events); HR = 0.68; 95% CI, 0.51–0.91; $P < .05$ OS: zoledronic acid (30 events) vs placebo (43 events); HR = 0.67; 95% CI, 0.41–1.07; $P = .09$	Positive: DFS Negative: OS
Coleman 2014[48] **AZURE**	3,360	Zoledronic acid q3–4wk × 6 doses then q3–6mo vs placebo × 5 yr (both pre- and postmenopausal)	7 yr	BM: zoledronic acid vs placebo (no. of events NR); HR = 0.81; 95% CI, 0.68–0.97; $P < .05$ DFS: zoledronic acid (473 events) vs placebo (493 events); HR = 0.94; 95% CI, 0.82–1.06; $P = .30$ OS: zoledronic acid (346 events) vs placebo (362 events); HR = 0.93; 95% CI, 0.81–1.08; $P = .37$	Positive: BM Negative: DFS and OS
Coleman 2013[49] **ZO-FAST**	1,035	Zoledronic acid immediate q6mo vs delayed initiation after T-score < 2 or fracture × 5 yr (postmenopausal)	5 yr	BM: zoledronic acid immediate (14 events) vs delayed (24 events); HR: NR DFS: zoledronic acid immediate (42 events) vs delayed (62 events); HR = 0.66; 95% CI, 0.44–0.97; $P < .05$ OS: zoledronic acid immediate (26 events) vs delayed (36 events); HR = 0.69; 95% CI, 0.42–1.14; $P = .15$	Positive: DFS Negative: OS

BM = bone metastasis; CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; NR = not reported; OS = overall survival.

Blanchette PS. Oncology (Williston Park). 2015;29(1):23-30,37

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Meta-Analysis

Table 5 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Meta-Analysis on Effects of Bisphosphonate Treatment on Recurrence and Cause-Specific Mortality in Early Breast Cancer by Menopausal Status

Premenopausal	**Bone Recurrence**	**Distant (Non-Bone) Recurrence**	**Breast Cancer Mortality**
Bisphosphonate	5.4% (170/3,134)	13.9% (435/3,134)	14.2% (445/3,134)
No bisphosphonate	6.0% (163/2,711)	14.3% (387/2,711)	15.7% (426/2,711)
Ratio of annual event rates ± standard error	0.93 ± 0.11	1.05 ± 0.08	1.00 ± 0.07
Perimenopausal	**Bone Recurrence**	**Distant (Non-Bone) Recurrence**	**Breast Cancer Mortality**
Bisphosphonate	6.1% (28/461)	8.2% (38/461)	9.1% (42/461)
No bisphosphonate	5.2% (19/367)	8.4% (31/367)	10.4% (38/367)
Ratio of annual event rates ± standard error	NR	NR	NR
Postmenopausal	**Bone Recurrence**	**Distant (Non-Bone) Recurrence**	**Breast Cancer Mortality**
Bisphosphonate	3.9% (222/5,737)	9.1% (523/5,737)	9.5% (544/9,332)
No bisphosphonate	5.4% (286/5,299)	10.1% (533/5,299)	11.4% (602/8,377)
Risk of annual event rates ± standard error	0.66 ± 0.08	0.92 ± 0.06	0.83 ± 0.06
Total	**Bone Recurrence**	**Distant (Non-Bone) Recurrence**	**Breast Cancer Mortality**
Bisphosphonate	4.5% (420/9,332)	10.7% (996/9,332)	11.0% (1,031/9,332)
No bisphosphonate	5.6% (468/8,377)	11.4% (951/8,377)	12.7% (1,066/8,377)
Risk of annual event rates ± standard error	0.77 ± 0.062 $2P = .0003$	0.98 ± 0.049 $2P > .1$; NS	0.90 ± 0.045 $2P = .03$

NR = not reported; NS = not significant. Adapted, with permission, from Coleman et al.[50]

Postmenopausal women

Beneficial effect for bisphosphonates in improving **breast cancer-related mortality** and **reducing risk of bone recurrence** (HR 0.83, $P = 0.004$ and HR 0.66, $P < 0.0001$, respectively.

No clear **benefit** was shown for **perimenopausal and premenopausal** women

Coleman R.Cancer Res. 2013;72:abstr S407.

Reason for the difference?

- reduced bone strength caused by menopause and aging may increase susceptibility to the development of metastasis
- the anticancer effects of bisphosphonates may be influenced by age- and estrogen-dependent changes to the local bone microenvironment

Reason for the difference?

- zoledronic acid has an antitumour effect in a subgroup of patients defined by a low oestrogen state—postmenopausal women, particularly those who are more than 5 years since menopause and hormone receptor-positive premenopausal women who are treated with a combination of GnRH agonist and antioestrogen therapy

Safety of bisphosphonates: side effects

- **bone pain**
- **fever**

- **hypocalcemia**
  - can be reduced by concurrent use of calcium and vitamin D supplements
- **osteonecrosis of the jaw**
  - with appropriate use of preventive dentistry, the rates of osteonecrosis of the jaw are less than 1%.
- **acute renal failure**
  - recommendation to modify the dosage in the presence of renal insufficiency and avoiding bisphosphonate therapy altogether if creatinine clearance is < 30 mL/min

Conclusion

- Bisphosphonates may be a useful adjunct to adjuvant systemic therapy for preventing breast cancer–related deaths in the subset of women who are postmenopausal
- Treatment may also be offered to premenopausal patients undergoing ovarian suppression
- The type of bisphosphonate required to produce this effect, as well as the dosing interval and duration of therapy, remains unclear
- Biomarkers needed to optimize patient selection