Evidence Profile 5.2.2. Comparison of Bisphosphonates

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Clodronate Ibandronate**	**Pamidronate Zoledronate**	**Clodronate Ibandronate**	**Pamidronate Zoledronate**		
Pain relief (categorical) (follow up: range 6 months to 2 years)												
2 [1,2]	RCT	serious [A]	not serious	not serious	not serious	sparse [B]	C 212 (1 study) I 65 (1 study)	P 171 (2 studies) Z 60 (1 study)	C 56/212 (26%) I 4/65 (6%)	P 40/171 (22% [C]) Z 9/60 (15%)	Low	CRITICAL
Pain relief (continuous) (follow up: range 6 months to 3 years; assessed with: BPI, VAS; Scale: 0 to 100 [worst]*)												
3 [2,3,4]	RCT	serious [D]	not serious	not serious	not serious	sparse [B]	C 68 (1 study) I 731 (2 studies)	P 62 (1 study) Z 774 (3 studies)	**Difference:** C -3.6 (-4.5, -2.7) I -3.3 (-4.2, -2.4)	**Difference:** P -4.2 (-4.9, -3.5) Z -5.0 (-5.5, -4.4)	Low	CRITICAL
Pain relief speed												
0									not estimable	not estimable		IMPORTANT
Pain reduction maintenance (follow up: range 6 months to 3 years)												
2 [2,3]	RCT	serious [D]	not serious	not serious	serious [E]	sparse [B]	C 68 (1 study) I 65 (1 study)	P 62 (1 study) Z 129 (2 studies)	**Difference:** C 13 (nd) mo I 5.5 (4.9, 6.0) mo	**Difference:** P 5.2 (4.7, 5.7) mo Z 7.4 (4.1, 10.6) [F] mo	Very Low	CRITICAL
Skeletal-related events, any (follow up: range 3 months to 3 year)												
2 [3,6]	RCT	serious [D]	not serious	not serious	serious [G]	sparse [B]	C 68 (1 study) I 27 (1 study)	P 0 Z 95 (2 studies)	C 14/68 (21%) I 7/27 (26%)	P nd Z 71/95 (18% [C])	Very Low	IMPORTANT
Skeletal-related events, fracture (follow up: range 3 months to 3 year)												
4 [1,2,3,4]	RCT	serious [D]	not serious	not serious	serious [G]	sparse [B]	C 280 (2 studies) I 796 (2 studies)	P 171 (2 studies) Z 826 (3 studies)	C 38/280 (11% [C]) I 119/769 (21% [C])	P 37/171 (27% [C]) [H] Z 109/826 (10% [C])	Very Low	IMPORTANT
Skeletal-related events, spinal cord compression (follow up: range 3 months to 3 year)												
3 [2,3,4]	RCT	serious [D]	not serious	not serious	serious [G]	sparse [B]	C 68 (1 study) I 769 (2 studies)	P 62 (1 study) Z 826 (3 studies)	C 1/68 (1.5%) [I] I 23/769 (2.9% [C])	P 7/62 (11%) Z 27/826 (3.1% [C])	Very Low	IMPORTANT
Skeletal-related events, bone radiation (follow up: range 3 months to 3 year)												
2 [3,4]	RCT	serious [D]	not serious	not serious	serious [G]	sparse [B]	C 68 (1 study) I 704 (1 study)	P 0 Z 766 (2 studies)	C 7/68 (10%) [J] I 210/704 (30%)	P nd Z 194/766 (18% [C])	Very Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clodronate Ibandronate	Pamidronate Zoledronate	Clodronate Ibandronate	Pamidronate Zoledronate		
Skeletal-related events, bone surgery (follow up: range 3 months to 3 year)												
3 [2,3,4]	RCT	serious [D]	not serious	not serious	serious [G]	sparse [B]	C 68 (1 study) I 769 (2 studies)	P 62 (1 study) Z 826 (3 studies)	C 0/68 (0%) [I] I 45/769 (5.9% [C])	P 4/62 (6.5%) Z 35/826 (3.8% [C])	Very Low	IMPORTANT
Skeletal-related events, hypercalcemia (follow up: range 3 months to 3 year)												
3 [2,3,4]	RCT	serious [D]	not serious	not serious	serious [G]	sparse [B]	C 68 (1 study) I 769 (2 studies)	P 62 (1 study) Z 826 (3 studies)	C 2/68 (2.9%) [I] I 104/769 (27% [C])	P 31/62 (50%) [K] Z 83/826 (12% [C])	Very Low	IMPORTANT
Quality of life												
0									not estimable	not estimable		CRITICAL
Functional outcomes												
0									not estimable	not estimable		IMPORTANT
Adverse events: Osteonecrosis of jaw												
3 [3,4,6]	RCT	serious [D]	not serious	not serious	very serious [L]	none	C 68 (1 study) I 731 (2 studies)	P 0 Z 792 (3 studies)	C 1/68 (1.5%) [M] I 5/731 (0.7% [C]) [M]	P nd Z 10/792 (1.2% [C]) [M]	Very Low	IMPORTANT

***Abbreviations**: **C:** clodronate; **CI**: confidence interval; **GI:** gastrointestinal; **I:** ibandronate; **mo**: months; **N/A**: not applicable; **nd**: no data; **NS**: not statistically significant; **P**: pamidronate; **RCT**: randomized controlled trial(s); **SRE**: skeletal-related event;*
***Z**: zoledronate.*

Explanations

A. Incomplete data reporting.
B. Sparse direct comparisons.
C. Meta-analyzed value.
D. Lack of blinding, incomplete data reporting.
E. Incomplete variance data.
F. Meta-analyzed value. Assumes standard deviation is the same in the study that did not report variance data as the study that did.
G. Small sample sizes for most comparisons.
H. von Au et al. reported significantly fewer fractures with pamidronate (7%) than clodronate (16%; P=0.033), but Choudhury et al. reported more (but statistically similar) fractures with pamidronate (47%) than ibandronate (29%) or ~~zolendronate~~zoledronate (25%).
I. In the same study, the rate in the zole~~n~~dro~~a~~nate group was 1/69 (1.4%), which was not significantly different.
J. In the same study, the rate in the zole~~n~~dro~~a~~nate group was 6/69(8.7%), which was not significantly different.
K. In the same study, the rate in the ibandronate group was 29/65 (45%), which was not significantly different (RR = 0.64; 95% CI 0.39, 1.03), but the rate in the ~~zolendronate~~zoledronate group was 17/60 (28%), which was significantly lower (RR = 0.57; 95% CI 0.35, 0.91).
L. Imprecise estimates for each comparison. See next footnote.
M. Ibandronate vs. ~~zolendronate~~zoledronate (2 studies): RR = 0.52 (95% CI 0.19, 1.45). Clodro~~a~~nate vs. ~~zolendronate~~zoledronate (1 study): RR = 3.09 (95% CI 0.12, 77.2).

Trials

1. von Au, A., Milloth, E., Diel, I., et al. Intravenous pamidronate versus oral and intravenous clodronate in bone metastatic breast cancer: a randomized, open-label, non-inferiority Phase III trial. Onco Targets Ther; 2016.
2. Choudhury, K. B., Mallik, C., Sharma, S., Choudhury, D. B., Maiti, S., Roy, C. A randomized controlled trial to compare the efficacy of bisphosphonates in the management of painful bone metastasis. Indian J Palliat Care; Sep 2011.

3. Wang, F., Chen, W., Chen, H., et al. Comparison between zoledronic acid and clodronate in the treatment of prostate cancer patients with bone metastases. Med Oncol; 2013.
4. Barrett-Lee, P., Casbard, A., Abraham, J., et al. Oral ibandronic acid versus intravenous zoledronic acid in treatment of bone metastases from breast cancer: a randomised, open label, non-inferiority phase 3 trial. Lancet Oncol; Jan 2014.
5. Rosen, L. S., Gordon, D. H., Dugan, W.,Jr., et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer; Jan 01 2004.
6. Francini, F., Pascucci, A., Bargagli, G., et al. Effects of intravenous zoledronic acid and oral ibandronate on early changes in markers of bone turnover in patients with bone metastases from non-small cell lung cancer. Int J Clin Oncol; Jun 2011.
7. Body, J. J., Lichinitser, M., Tjulandin, S., Garnero, P., Bergstrom, B. Oral ibandronate is as active as intravenous zoledronic acid for reducing bone turnover markers in women with breast cancer and bone metastases. Ann Oncol; Jul 2007.