Evidence Profile 5.2.1. Bisphosphonates vs. Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bisphosphonates	Placebo	Relative (95% CI)	Absolute (95% CI)		
Pain Relief (categorical), complete (follow up: range 24 weeks to 6 months)												
3 [1,2,3]	RCT	not serious	not serious	serious [A]	not serious	none	22/84 (27% [B])	14/88 (16% [B])	**RR 1.61** (0.89, 2.93)	**97 more per 1000** (from 18 fewer to 306 more)	Moderate	CRITICAL
Pain Relief (categorical), improvement (follow up: range 4 weeks to 48 months; assessed with PPI 0-100 [worst] [C])												
4 [4,5,6,7]	RCT	not serious	not serious	serious [A]	not serious	none	61/210 (22% [B])	50/232 (16% [B])	**RR 1.24** (0.90, 1.71)	**38 more per 1000** (from 16 fewer to 113 more)	Moderate	CRITICAL
Pain Relief (continuous) (follow up: range 1 week to 96 weeks)												
14 [7,8,9,10,11,12,13,14,15,16,17,18,19,20]	RCT	not serious	not serious	serious [A]	not serious	none	1174	1196	**Net Diff -11.8** (-17.6, -6.12), favoring bisphosphonate		Moderate	CRITICAL
Pain relief speed												
0									not estimable			IMPORTANT
Pain reduction maintenance (follow up: 3 years)												
1 [21]	RCT	serious [D]	N/A	not serious	not serious	single study	283	286	**HR 1.27** (0.84, 1.92) 3.4 vs. 5.5 months		Low	CRITICAL
Skeletal Related Events, any (follow up: range 1 year to 7 years)												
20 [8,9,10,11,14,20,22,23,24,25,26,27,28,29,30,31,32,33,34,40]	RCT	serious [E]	not serious	not serious	not serious	none	**Any SRE (RR)** 1571/3569 (44% [B,F])	1621/2989 (54% [B,G])	**RR 0.81** (0.76, 0.86)	**104 fewer per 1000** (from 76 to 130 fewer)	Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bisphosphonates	Placebo	Relative (95% CI)	Absolute (95% CI)		
							Any SRE (HR) 1604	1325	**HR 0.71** (0.61, 0.84)			
Skeletal Related Events, fracture (follow up: range 27 weeks to 72 months)												
12 [9,10,11,14,20,24,26,27,34,35,36,37]	RCT	serious [E]	not serious	not serious	not serious	none	386/1972 (20% [B,H])	467/1561 (30% [B,I])	**RR 0.75** (0.67, 0.84)	**58 fewer per 1000** (from 37 to 77 fewer)	Moderate	IMPORTANT
Skeletal Related Events, spinal cord compression (follow up: range 27 weeks to 72 months)												
8 [9,10,11,14,24,27,34,36]	RCT	serious [E]	not serious	not serious	not serious	none	42/1464 (2.9% [B,J])	50/1211 (4.1% [B,K])	**RR 0.74** (0.49, 1.12) [L]	**11 fewer per 1000** (from 4 more to 21 fewer)	Moderate	IMPORTANT
Skeletal Related Events, radiotherapy (follow up: range 6 months to 3 years)												
12 [9,10,14,24,26,27,28,30,34,35,37,38]	RCT	serious [E]	not serious	not serious	not serious	none	471/1944 (24% [B,M])	573/1694 (34% [B,N])	**RR 0.71** (0.63, 0.81)	**76 fewer per 1000** (from 47 to 102 fewer)	Moderate	IMPORTANT
Skeletal Related Events, bone surgery (follow up: range 27 weeks to 2 years)												
9 [9,10,14,27,30,34,35,37,39]	RCT	serious [E]	not serious	not serious	not serious	none	77/1744 (4.4% [B,O])	110/1488 (7.4% [B,P])	**RR 0.62** (0.44, 0.89) [Q]	**22 fewer per 1000** (from 1 to 36 fewer)	Moderate	IMPORTANT
Skeletal Related Events, hypercalcemia (follow up: range 6 months to 3 years)												
13 [9,10,11,14,25,26,27,28,30,34,35,37,38]	RCT	serious [E]	not serious	not serious	not serious	none	81/1497 (5.4% [B,R])	188/1522 (12% [B,S])	**RR 0.47** (0.37, 0.60) [T]	**59 fewer per 1000** (from 43 to 71 fewer)	Moderate	IMPORTANT
Quality of Life (follow up: range 6 months to 2 years; assessed with EORTC QLQ-C30, FACT-P; Scale: 0-100 [best] [B])												
5 [7,11,20,21,29]	RCT	not serious	serious [U]	serious [V]	serious [W]	none	3521	3005	**Net Difference 8** (-6, 22), favoring bisphosphonate		Very Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bisphosphonates	Placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (follow up: 59 months [months]; worsened WHO performance status by at least one grade)												
1 [21]	RCT	not serious	N/A	not serious	not serious	single study	79/155 (51%)	98/156 (63%)	**RR 0.81** (0.67, 0.99) **HR 0.71** (0.56, 0.92), favoring bisphosphonate		Moderate	CRITICAL
Functional Outcomes (follow-up: 24 months; assessed with ECOG performance status, scale 0 to 100 [best] [B])												
1 [14]	RCT	not serious	N/A	not serious	serious [X]	single study	119	104	**Net Diff -7.7** (-17.0, 1.7), favoring pamidronate		Low	IMPORTANT
Functional Outcomes (follow-up 24 months; assessed with FACT-P Physical Well-Being Score, scale 0 to 100 [best] [B])												
1 [28]	RCT	serious [X]	N/A	serious [V]	serious [Y]	single study	2993	2901	**Diff 1.4** (0.5, 3.3), [Z] favoring pamidronate		Very Low	IMPORTANT
Functional Outcomes (follow-up 24 months; assessed with FACT-P Social Well-Being Score, scale 0 to 100 [best] [B])												
1 [28]	RCT	serious [X]	N/A	serious [V]	serious [Y]	single study	3000	2914	**Diff 1.8** (1.0, 2.6), [Z] favoring pamidronate		Very Low	IMPORTANT
Functional Outcomes (follow-up 24 months; assessed with FACT-P Functional Well-Being Score, scale 0 to 100 [best] [B])												
1 [28]	RCT	serious [X]	N/A	serious [V]	serious [Y]	single study	3000	2914	**Diff 1.8** (0.6, 2.9), [Z] favoring pamidronate		Very Low	IMPORTANT
Adverse Events: Osteonecrosis of jaw (1 to 4 years)												
4 [6,19,24,34]	RCT	not serious	not serious	not serious	serious [AA]	no events	0/460 (0%)	0/450 (0%)	not estimable		Low	IMPORTANT

Abbreviations: CI: *Confidence interval;* ***Diff****: difference (between groups);* ***EORTC QLQ-C30****: European Organization for Research and Treatment of Cancer Quality Of Life Questionnaire Core-30;* ***FACT****: Functional Assessment of Cancer Therapy;* ***GI****: gastrointestinal;* ***HR****: hazard ratio;* ***N/A****: not applicable;* ***NS****: not statistically significant;* ***PPI****: Present Pain Intensity;* ***RCT****: randomized controlled trial(s);* ***RR****: relative risk (log scale);* ***SRE****: skeletal-related events.*

Explanations

A. Unclear whether measured pain was overall cancer pain or metastatic bone pain
B. Meta-analyzed value.
C. Scales transformed to 0 to 100, as necessary.
D. Unblinded

E. Issues with lack of blinding, poor allocation concealment, and poor reporting.
F. Median 45% (Range 4.6-60).
G. Median 54% (Range 5.3, 91).
H. Median 15% (Range 0, 45).
I. Median 21% (Range 3.2, 54).
J. Median 3.0% (Range 0, 3.8).
K. Median 4.0% (Range 1.7, 12).
L. Pamidronate studies were nonsignificant with RR 1.07 (0.60, 1.90) but Zoledronate studies had RR 0.52 (0.27, 0.99) However, the difference in effect between the two sets of studies was nonsignificant (P=0.072).
M. Median 20% (Range 8.8-40).
N. Median 32% (Range 7.8-48).
O. Median 4.3% (Range 0-7.1).
P. Median 6.7% (Range 0.9-12).
Q. The subset of pamidronate studies were statistically significant in contrast to the ~~zolendronate~~zoledronate studies (P=0.041 between bisphosphonates). See Forest Plot 5.2.2 SRE Surgery.
R. Median 4.4% (Range 0-24).
S. Median 10% (Range 1.1-35).
T. The three subsets of studies based on medication used were not significantly different than each other; however, the three ~~zolendronate~~zoledronate studies had a stronger effect than the other two medications, although the difference was not statistically significant (P=0.072). See Forest Plot 5.2.2 SRE Hypercalcemia.
U. Wide range of normalized net differences, from -3.2 to 31 (where 100=best). Significant statistical heterogeneity.
V. EORTC and FACT (total score) are measures of quality of life that mix concepts of both quality of life and functional outcomes. The systematic review treated the total scores as quality of life measures and the relevant subscores as functional outcomes, but these do not cleanly measure function.
W. Highly imprecise. Two studies reported only median values and ranges.
X. Small study.
Y. Issues with lack of blinding and poor reporting.
Z. Difference and confidence interval estimated from reported data, but study implied no significant difference.
AA. Not estimable.

Trials

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