Efficacy and Safety of Bone Management Agents Administered at 12 Weeks vs. 4 Weeks in Patients with Bone Metastases: A Systematic Review

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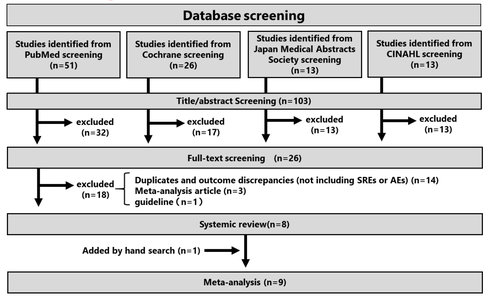
Background: Bone Modifying Agents (BMAs) have been used to prevent skeletal-related events (SRE) in cancer patients with bone metastases. In this meta-analysis, efficacy and adverse events (AEs) were studied based on a de-escalation strategy in which the BMA dosing interval was prolonged from 4 to 12 weeks.

Methods: PubMed, Cochrane, ICHUSHI, and CINAHL were searched for articles on BMA dosing intervals from outcomes measured were the incidence of SRE and related various AEs. A quantitative meta-analysis was performed using a random-effects model to calculate relative risk ratios (RR) and 95% confidence intervals (CI).

Selection process for articles



Key Results

- The meta-analysis included three randomized controlled studies (RCTs) of Zoledronic acid hydrate (ZA) (n = 2,663) and six RCTs (n = 141) on BMA other than ZA.
- There was no difference in the incidence of SREs when comparing the dosing frequency of 12 versus 4 weeks for BMA (RR = 1.21, 95% CI [0.82-1.78], p = 0.33).
- AEs related to treatment discontinuation were significantly less frequent with ZA given every 12 weeks than when given every 4 weeks (RR = 0.51 [0.30-0.89], p = 0.02).
- Renal dysfunction leading to grade ≥3 or discontinuation of treatment with ZA occurred significantly less frequently with every 12-week dosing (RR = 0.33 [0.12-0.91], p = 0.03).

Details of studies included in the meta-analysis

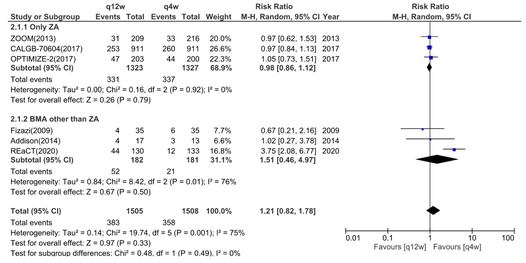
Study	Design	N	Disease (history of BMA use)	BMA	Study period	Primary endpoints	Secondary endpoints	SRE or SSE*	AEs	Renal dysfunction	ONJ	Hypocalcemia	Others
CALGB -70604[1)]	RCT non-inferiority trial	1,822	Prostate, Multiple myeloma (8-9% patient used any BMA)	ZA	2 year	SRE	BPI, ECOG-PS, ONJ, Renal dysfunction, SMR	260/911(29%) vs 253/911(28%)	Treatment discontinuation AE：42/911(5%) vs 18/911(2%)	Increased serum creatinine of ≥0.5 mg/dL：174/875(20%) vs 137/882(16%) Severe renal dysfunction（Grade ≥3 elevated serum creatinine level)：10/852(1.2%) vs 4/837(0.5%)	18/911(2.0%) vs 9/911(1.0%)	Any grade: 329/866(38%) vs 298/851(35%) Grade4: 8/866(1%) vs 5/851(1%)	
OPTIMIZE-2[2)]	RCT non-inferiority trial	416	Breast (All patient used ZA and/or PA)	ZA	1 year	SRE	Bone pain, BPI, analgesic consumption), metabolic bone markers, Safety	44/200(22%) vs 47/203(23%)	Any grade：189/198(96%) vs 189/202(94%) Grade 3-4：94/198(47%) vs 86/202(43%) Serious AE：50/198(25%) vs 51/202(25%) Treatment discontinuation AE：23/198(12%) vs 18/202(9%)	Any grade：19/198(10%) vs 16/202(8%) Treatment discontinuation: 6/198(3%) vs 1/202(1%)	2/198(1%) vs 0/202(0%)		Nausea: 59/198(30%) vs 53/202(26%) vomiting: 32/198(16%) vs 34/202(17%) Bone pain: 49/198(25%) vs 48/202(24%)
ZOOM[3)]	RCT non-inferiority trial	425	Breast (All patient used ZA)	ZA	1 year	SRE	Bone pain, analgesic use, NTx, safety	33/216(15%) vs 31/209(15%)	Any grade：184/216(85%) vs 159/209(76%) Grade 3-4：95/216(44%) vs 92/209(44%) Serious AE：29/216(13%) vs 21/209(10%) Treatment discontinuation AE：9/216(4%) vs 2/209(1%)	Any grade：2/216(1%) vs 1/209(<1%)	3/216(1%) vs 4/209(2%)		Nausea: 33/216(15%) vs 24/209(11%) vomiting: 23/216(11%) vs 14/209(7%) Bone pain: 65/216(31%) vs 56/209(27%)
REFORM[4)]	RCT	30	Breast (All patient used PA)	PA	2year	CTx, BSAP	BPI, FACT-BP	3/13(23%) vs 4/17(24%)					
REaCT[5)]	RCT non-inferiority trial	263	Breast, Prostate(48% patient used any BMA)	Dmab(56%) ZA(24%) PA(20%)	2year	HRQoL, QLQ-C30	Pain, SSE, tSSE	12/133(9%) vs 44/130(34%) *	Treatment discontinuation AE：22/133（17%）vs 31/130（24%）	Any grade：4/133（3%） vs 4/130（3%）	1/133(1%) vs 1/130(1%)	Any grade: 3/133(2%) vs 3/130(2%)	
Fizazi.k[6)]	RCT	111	Breast, Prostate (82% patient used ZA)	ZA or PA(q4w) Dmab(q4w→q12w)	13W-25W	NTx(13W)	CTx, NTx (25W)	6/35(17%) vs 4/35(11%)					
Lipton（2007）[7)]	RCT	255	Breast cancer (No use BP)	Dmab(q4w or q12w), BP(ZA, PA, IN)(q4w)	13W	NTx	Patient with -65% decrease in NTx, SRE, safety		Any grade：155/169(92%) vs 76/85(89%) Serious AE：28/169(17%) vs 12/85(14%) Treatment discontinuation AE: 41/169(24%) vs 13/85(15%)				
Lipton（2008）[8)]	RCT	255	Breast cancer (No use BP)	Dmab(q4w or q12w), BP(ZA, PA, IN)(q4w)	13W	NTx	NTx (25W)		Any grade：41/43(95%) vs 82/85(96%) Serious AE：15/43(35%) vs 29/85（34%） Treatment discontinuation AE: 1/43(2%) vs 4/85(5%)				
REDUCE[9)]	RCT	101	Prostate cancer	Dmab	3.5years (interim analysis)	SSE	hypocapnia					Any grade: 23/57(40%) vs 15/44(34%)	

Each incidences were shown to q4w vs q12w. ZA: zoledronic acid, Dmab: denosumab, PA: pamidronic acid, N: Number of patients, AEs: Adverse events, HRQoL: Health-related quality of life, QLQ-C30: The European Organization for Research and Treatment of Cancer QLQ-C30, CTx: crosslinked N-terminal telopeptide type I collagen, BSAP: bone-specific alkaline phosphatase, BPI: brief pain inventory, NTx: type I collagen N-terminal telopeptide, BMA: bone modifying agents; FACT-BP :Functional Assessment of Cancer Therapy Bone Pain, SMR: Skeletal morbidity rate, SRE: skeletal-related events, SSE: symptomatic skeletal events. tSSE: time to symptomatic skeletal events, ONJ: osteonecrosis of the jaw, RCT: randomized controlled trial, BP: bisphosphonates

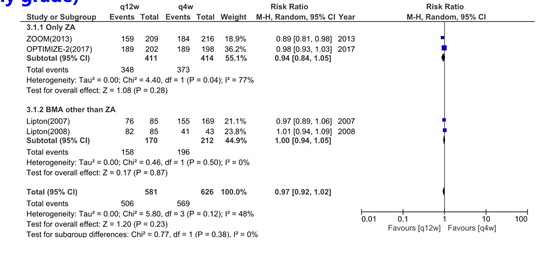
1)JAMA 2017;317:48-58., 2)JAMA Oncol 2017;3:906-12, 3)Lancet Oncol 2013;14:663-70, 4)Springerplus 2014;3:577, 5)Eur J Cancer 2021;142:132-40, 6)J Clin Oncol 2009;27:1564-71, 7)J Clin Oncol 2007;25:4431-7, 8)Clin Cancer Res 2007;14:6690-6, 9)Eur Soc Med Oncol 2014;25(Suppl 4):540.

Forest plot of studies including ZA only or BMA other than ZA comparing 4-weeks vs 12-weeks dosing schedule

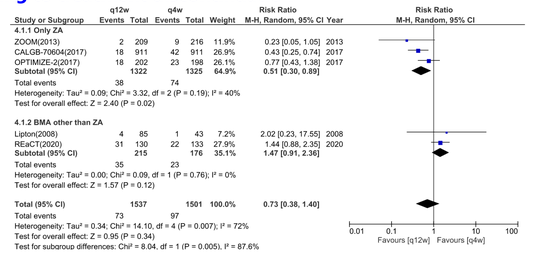
SRE



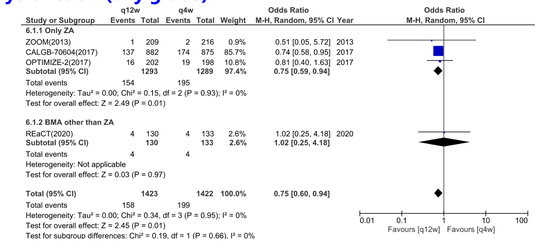
AEs(any grade)



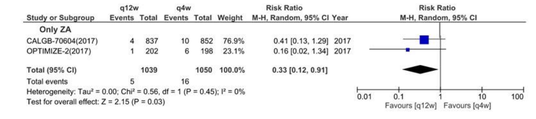
AE leading to treatment discontinuation



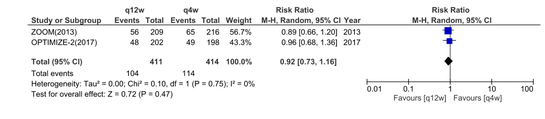
Renal dysfunction (any grade)



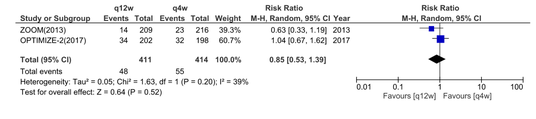
Renal dysfunction (grade≧3 or treatment discontinuation)



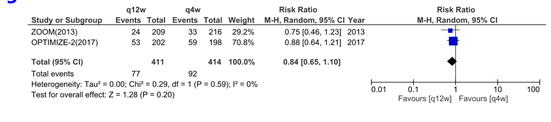
Bone pain



Nausea



Vomiting



Conclusion: This meta-analysis showed no influence of BMA de-escalation on the incidence of SRE, nevertheless, AEs appeared to reduce with the de-escalated usage of ZA. Prolonging the BMA dosing interval from 4 to a maximum of 12 weeks is a beneficial treatment strategy that reduces the risk of renal dysfunction without increasing SRE.