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Adjuvant bisphosphonates or RANK-ligand inhibitors for patients with breast cancer and bone metastases: A systematic review and network meta-analysis

Y. Tesfamariam[a,1], T. Jakob[a,1], A. Wöckel[b], A. Adams[c], A. Weigl[a], I. Monsef[a], K. Kuhr[c,1], N. Skoetz[a,*,1]

[a] Department I of Internal Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany
[b] Department for Gynecology and Obstetrics, University Hospital Würzburg, Würzburg, Germany
[c] Institute of Medical Statistics and Computational Biology, University of Cologne, Cologne, Germany

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ABSTRACT

Bone-modifying agents like bisphosphonates and receptor activator of nuclear factor kappaβ ligand (RANK-L) inhibitors are used as supportive treatments in breast cancer patients with bone metastases to prevent skeletal-related events (SREs). Due to missing head-to-head comparisons, a network meta-analysis was performed to provide a hierarchy of these therapeutic options. Through a systematic literature search, 21 randomized controlled trials (RCTs) that fulfilled the inclusion criteria were identified. To prevent SREs, the ranking through *P*-scores showed denosumab (RR: 0.62; 95%CI: 0.50-0.76), zoledronic acid (RR: 0.72; 95%CI: 0.61-0.84) and pamidronate (RR: 0.76; 95%CI: 0.67-0.85) to be significantly superior to placebo. Due to insufficient or heterogeneous data, overall survival, quality of life, pain response and adverse events were not able to be analyzed within the network. Although data were sparse on adverse events, the risk of significant adverse events appeared low. The results of this review can therefore be used to formulate clinical studies more precisely in order to standardise and focus on patient-relevant outcomes.

1. Introduction

Breast cancer is the most common type of cancer affecting women worldwide. Also it remains the leading cause of cancer related deaths in women, despite the rapid advances in early detection and specific treatments (Monnot and Romero, 2017). As of 2014, an estimated 3,327,552 women were living with breast cancer in the United States and 266,120 new cases of breast cancer are estimated to be reported in 2018 with 40,920 expected to result in death (Howlader et al., 1975). In breast cancer, fast proliferating and migrating cells act as precursors for the establishment of invasive breast tumors, which can furthermore progress into a metastatic disease affecting the axillary breast nodes and most often spreading to distant locations, in particular the bone and bone marrow (Shiozawa et al., 2015).

Metastatic spread is the leading cause of breast cancer related deaths and is known to vary considerably in its timing and distribution between individual patients. Bone metastases are classified according to radiographic appearance as osteolytic, osteoblastic or mixed, with the majority of breast cancer patients having osteolytic lesions (Roodman, 2004). As a result patients are at high risk of complications such as hypercalcemia, fractures and spinal cord compressions, which result in pain and reduced patient mobility (Healey and Brown, 2000). Collectively, these events are defined as skeletal-related events (SREs) which include: pathologic fractures, spinal cord compression, necessity for radiation to bone (for pain or impending fracture) or surgery to bone (So et al., 2012).

Even though breast cancer metastases were found to be clinically evident in approximately 5% of women at the time of diagnosis, the majority of patients develop metastases years or even decades later making early diagnosis, prevention or treatment difficult (Schwartz and Erban, 2017). Up to date, no standard cancer treatment has been established for patients with metastatic breast cancer, as individual patient based factors such as specific tumor biology, growth rate of disease, presence of visceral metastases, history of prior therapy and response and risk for toxicity collectively influence the treatment strategy (O'Shaughnessy, 2005). Hence, currently available treatments

* Corresponding author at: Department I of Internal Medicine University Hospital Cologne, Kerpener Str. 62, 50937, Cologne, Germany.
E-mail address: nicole.skoetz@uk-koeln.de (N. Skoetz).
[1] Equal contribution.

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are only of palliative nature with the aim of delaying disease progression, improving patient's quality of life and prolonging overall survival rate.

Over the past years, bone-modifying agents such as bisphosphonates and receptor activator of nuclear factor kappaB ligand (RANK-L) inhibitors, that target cancer related bone loss, have been developed and made available for physicians treating breast cancer patients with bone metastases. Bisphosphonates reduce bone resorption via two main mechanisms that directly inhibit the highly specialized bone resorbing osteoclast cells. The first group of bisphosphonates including clodronate, work by inhibiting ATP dependent intracellular enzymes, whereas the second group of bisphosphonates such as pamidronate and zolendronic acid work by inhibiting enzymes of the mevalonate pathway, both effectively preventing the signaling pathways of key regulatory proteins involved in osteoclast formation (Coxon et al., 2000; Rogers et al., 1999; Ross et al., 2003; Russell et al., 1999). Denosumab, a RANK-L inhibitor on the other hand, is a monoclonal antibody that directly reduces the osteoclastogenesis by inhibiting the RANK/RANK-L pathway responsible for the maturation of osteoclast precursors into osteoclasts (Bartsch et al., 2010). Several randomized controlled trials (RCTs) indicated the efficacy of bisphosphonates in reducing bone pain and skeletal morbidity in patients with breast cancer and multiple myeloma, whereas denosumab treatment demonstrated to significantly increase bone mineral density, effectively reducing the risk of fracture in patients (Anastasilakis et al., 2009; Coleman, 2008). However, despite the reduction in SREs, osteonecrosis of the jaw (ONJ) was reported as an adverse event in 1.7% of patients receiving denosumab and in 0.10% of patients receiving bisphosphonates (Hellstein et al., 2011; Qi et al., 2013).

Currently, due to the absence of established international guidelines with recommendations and consistent approach strategies to the use of bone-modifying agents, the decision making process regarding prevention or treatment of skeletal complications in breast cancer patients with bone metastases is difficult for both patients and physicians (Ripamonti et al., 2012; Van Poznak et al., 2011). Therefore we conducted a systematic review and a network meta-analysis that summarizes direct and indirect comparisons in order to provide sufficient evidence from randomized head-to-head comparisons of various types of bisphosphonates and RANK-L inhibitors. The aim of the review was to provide a comprehensive overview on the benefits and harms of different bisphosphonates and RANK-L inhibitors and establish a hierarchy of therapeutic options.

2. Methods

This review was registered with the International prospective register of systematic reviews (PROSPERO 2015 CRD42015026077).

2.1. Search strategies for identification of studies

Search strategies were developed according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011) for the following databases without language restriction: the Cochrane Library including the Cochrane Central Register of Controlled Trials (CENTRAL; issue 2016), MEDLINE (OVID; 1980–2016), conference proceedings of annual meetings of the American Society of Clinical Oncology (ASCO), San Antonio Breast Cancer Symposium if not included in CENTRAL. Moreover, a trial register was searched for completed but not published trials (http://www.controlled-trials.com/mrct).

2.2. Inclusion criteria

We only included RCTs analyzing patients with confirmed breast cancer and bone metastases, irrespective of age of patients and type of antineoplastic therapy, assessing interventions of adjuvant bisphosphonates or RANK-ligand inhibitors of any type. Quasi-randomized trials (e. g. treatment allocation alternate or by date of birth) and crossover trials were excluded.

2.3. Study selection, data extraction and quality assessment of included studies

Four authors (YT, TJ, NS and AW) independently in doubles screened titles and abstracts of the studies identified by the search strategies for eligibility according to the inclusion criteria. For data extraction and quality assessment of included studies full text versions were used. Data extractions were also done independently by four authors in doubles (YT, TJ, NS and AW) using a standardized data extraction form which contained the following items: study characteristics, patient characteristics, intervention, outcome data and study quality. Quality of the studies was assessed independently by the same authors by judging the risk of bias. Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), as well as outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other biases were assessed (Higgins et al., 2011). In case of missing data, authors of primary studies were contacted for additional information. All qualified studies were referenced as full text publications in order to both extract the data and to evaluate the quality of the studies.

2.4. Outcome measurements

In this systematic review and network meta-analysis overall survival was the primary outcome. Quality of life and pain were assessed as secondary outcomes along with osseous complications such as pathologic fractures, spinal cord compression and hypercalcemia, which were recorded within the outcome SREs. In addition, adverse events were systematically evaluated, to allow an overall analysis of the benefits and harms associated with each therapy. Only trials reporting at least one of the outcomes of interest were included. Trials not reporting any of these outcomes were excluded.

2.5. Statistical analysis

As the measure of treatment effect, we used hazard ratios (HRs) with 95% confidence intervals (CIs) for time-to-event data, risk ratios (RR) with 95% CIs for binary data and mean differences (MD) with 95% CIs for continuous data. In case different instruments were used to assess effects in continuous outcomes, we used standardized mean differences (SMD). If necessary, HRs were calculated using the methods described by Tierney (Tierney et al., 2007). We used the statistical software package R for meta-analytical calculations (R-Core-Team, 2018). Network plots were created using the CINeMA Software (Martin et al., 2017).

A network meta-analysis summarizes direct and indirect evidence for different treatments of interest and allows generating a clinically meaningful treatment ranking according to their safety and efficacy. To explain the meaning of direct and indirect evidence, assume a setting with two active treatments, A and B, and a comparator treatment C. Head-to-head trials A versus C and B versus C provide direct evidence regarding the difference of treatment effects for A and C; and B and C, respectively. In addition, these trials provide indirect evidence regarding the difference of treatment effects A and B. So in case of lacking head-to-head comparisons, two treatments can be compared via a common comparator to generate indirect evidence. To detect possible inconsistencies between direct and indirect evidence in a full network, the consistency between direct and indirect evidence evaluated, if possible. To achieve valid results, three important assumptions have to be met: First, included trials need to be comparable with respect to possible effect modifiers such as study characteristics and patient

characteristics (transitivity assumption). Second, effect estimates of studies comparing the same interventions, i.e. studies with the same design, are not too heterogeneous (homogeneity assumption). Third, indirect evidence on a comparison in the network do not differ from direct evidence (consistency assumption) (Song et al., 2009; Higgins et al., 2012).

We performed a frequentist network meta-analysis (Rücker, 2012a) using the R package "netmeta" (Rücker et al., 2018). Network plots were used to evaluate the extent to which treatments are connected. For each comparison, we gave the estimated treatment effect along with its 95% CI (random effects model). Results were presented graphically using forest plots with reference treatment "placebo" or "no treatment". To show the treatment hierarchy, forest plots were sorted by *P*-scores. *P*-scores allow ranking treatments on a continuous 0 (worst) to 1 (best) scale in a frequentist network meta-analysis (Rücker and Schwarzer, 2015). The transitivity assumption was evaluated epidemiologically by comparing the distribution of study characteristics and patient characteristics across the different pairwise comparisons. To evaluate the presence of heterogeneity and inconsistency, we calculated the generalized heterogeneity statistic Q_{total} and the generalized I^2 statistic, as described in Schwarzer 2015 (Schwarzer et al., 2015). We used the decomp.design function of "netmeta" package for decomposition of the heterogeneity statistic into a Q statistic for assessing the heterogeneity between studies with the same design and a Q statistic for assessing design inconsistency, thus we were able to identify the amount of heterogeneity/inconsistency within and between designs. In addition, the presence of inconsistency was evaluated locally by comparing direct and indirect treatment estimates for each closed loop formed by the network of trials by using the netsplit function of "netmeta" package.

Pairwise comparisons were part of the network meta-analyses. However, in order to outline available direct evidence, we provide forest plots of standard pairwise meta-analyses in addition (random effects model, using the R package "meta") (Schwarzer, 2007). Heterogeneity among trials was tested using Cochran's Q based on a chi-squared statistic and quantified using the I^2 statistic (Higgins et al., 2003). The presence of small study effects was examined graphically by generating funnel plots for pairwise comparisons with at least ten trials. Linear regression tests were used to test for funnel plot asymmetry (Egger et al., 1997). All presented *P*-values are two sided unless stated otherwise. *P*-values less than 0.05 were considered significant for this test.

3. Results

3.1. Results of the search and the study selection process

The sensitive, highly complex search strategy resulted in a database of 1619 identified references. Of these references, 72 doubles and 1099 references were immediately excluded as they did not meet the inclusion criteria. The remaining 448 references were screened as full texts. 427 references were excluded because they did not report as RCT, did not report separate data for breast cancer patients, did not investigate the interventions of interest, or intervene in breast cancer patients without metastasis.

A total of 39 references were included in the review (21 studies). The study by Luedders et al. only examined laboratory values to detect nephrotoxicity. Since no other outcomes were reported, this study could not be included in the meta-analysis (Luedders et al. (2015)). The study of Heras et al. did not report on the randomisation of the 150 enrolled patients therefore it was excluded from the final analysis (Heras et al., 2009). Therefore these two were not involved in the quantitative analysis. The different steps involved in including or excluding references are shown in Fig. 1 according to the PRISMA Reporting Guidelines (Moher et al., 2009).

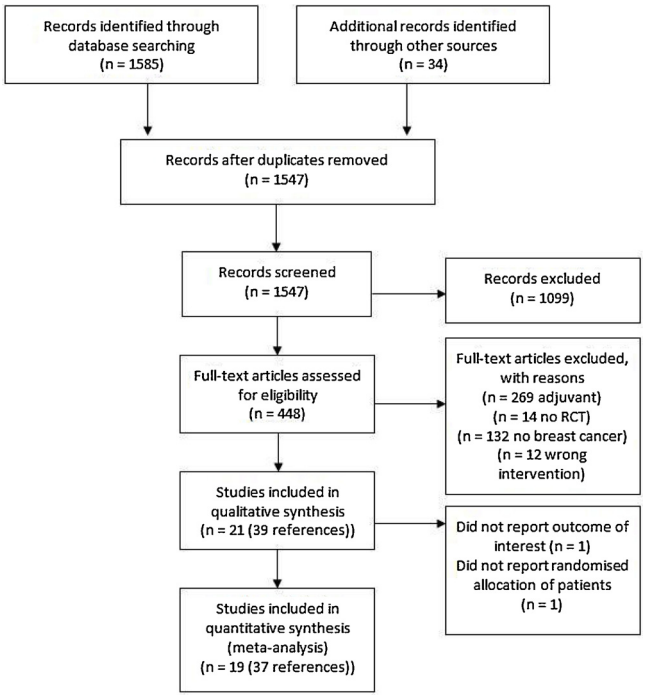

Fig. 1. PRISMA flow-chart.

3.2. Description of the included studies

The 21 included studies examined a total of 9048 patients. The smallest study evaluated 33 patients whereas the largest study evaluated 2046 patients. 17 studies were two-armed, 3 studies three-armed and 1 study four-armed. A detailed description of the interventions can be found in Table 1. Treatment arms with different dosages and mode of application such as intravenous or oral administration were pooled together and merged prior to analysis. The included studies were similar in clinical and methodological features which could influence the relative treatment effects, so we assumed that the transitivity assumption holds. The overall risk of bias was judged as low to unclear. For a detailed overview see Fig. 2.

3.3. Network

From the included studies, a network was constructed that formed the basis of our network meta-analysis. For an ideal network with evidence for all direct and indirect comparisons see Fig. 3. The data from all included studies resulted in seven different treatment options that were directly or indirectly compared.

3.4. Presentation of the results per outcome

3.4.1. Overall survival

Ten of the included studies reported overall survival of patients (Elomaa et al., 1988; van Holten-Verzantvoort et al., 1991; Hortobagyi et al., 1996; Kristensen et al., 1999; Theriault et al., 1999; Tripathy et al., 2004; Stopeck et al., 2010; Barrett-Lee et al., 2014; Conte et al., 1996). However, only two studies gave HRs with corresponding 95% CIs for pairwise comparisons of treatments (Stopeck et al., 2010; Barrett-Lee et al., 2014). There was neither a difference in overall survival for zoledronic acid compared to denosumab HR 0,95 (95% CI 0,81 to 1,11; *p*-value = 0,49) (Stopeck et al., 2010), nor for ibandronate compared to zoledronic acid: 1,086 (95% CI 0,948 to 1,245, *p*-value = 0,24) (Barrett-Lee et al., 2014). Seven of the nine studies reported results median overall survival (van Holten-Verzantvoort et al., 1991; Hortobagyi et al., 1996; Kristensen et al., 1999; Theriault et al.,

Table 1
Characteristics of included studies.

Reference	Year	Study Arms	*N* of patients	Median Age in years (Range)	Drug regimen
(Elomaa et al., 1983)	1983	Arm1: Clodronate	Arm1: 17	Arm1: 52 (34-69)	1600-3200 mg orally
		Arm2: Placebo	Arm2: 17	Arm2: 50 (36-68)	
(Martoni et al., 1991)	1991	Arm1: Clodronate	Arm1: 17	Arm1: 57 (42-78)	300 mg daily I.V
		Arm2: Placebo	Arm2: 16	Arm2: 59 (39-73)	
(van Holten-Verzantvoort et al., 1991)	1991	Arm1: Pamidronate	Arm1: 81	Arm1: 61	300 mg orally
		Arm2: No treatment	Arm2: 80	Arm2: 61.4	
(Paterson et al., 1993)	1993	Arm1: Clodronate	Arm1: 85	Arm1: 58 (26-77)	1600 mg
		Arm2: Placebo	Arm2: 88	Arm2: 61 (33-74)	
(Conte et al., 1996)	1996	Arm1: Pamidronate	Arm1: 143	Arm1: 58 (30-79)	45 mg
		Arm2: No treatment	Arm2: 152	Arm2: 58 (31-78)	
(Hortobagyi et al., 1996)	1996/	Arm1: Pamidronate Disodium	Arm1: 185	Arm1: 57	90 mg I.V
	1998	Arm2: Placebo	Arm2: 195	Arm2: 56	
(Hultborn et al., 1999)	1999	Arm1: Pamidronate	Arm1: 201	Arm1: 60	60 mg I.V
		Arm2: Placebo	Arm2: 203	Arm2: 61	
(Kristensen et al., 1999)	1999	Arm1: Clodronate	Arm1: 48	Arm1: 53 (34-74)	800 mg orally
		Arm2: No treatment	Arm2: 51	Arm2: 53 (34-71)	
(Theriault et al., 1999)	1999	Arm1: Pamidronate Disodium	Arm1: 182	Arm1: 60	90 mg I.V
		Arm2: Placebo	Arm2: 189	Arm2: 62	
(Rosen et al., 2001)	2001	Arm1: Zoledronic acid	Arm1: 378	Arm1: 58	Arm 1: 4 mg
		Arm2: Zoledronic acid	Arm2: 364	Arm2: 58	Arm 2: 8/4 mg
		Arm3: Pamidronate	Arm3: 388	Arm3: 56	Arm 3: 90 mg I.V
(Berenson et al., 2001)	2001	Arm1: Zolendronic acid	Arm1: 68	Arm1: 58	Arm 1: 0.4 mg
		Arm2: Zolendronic acid	Arm2: 73	Arm2: 56	Arm 2: 2 mg
		Arm3: Zolendronic acid	Arm3: 66	Arm3: 60	Arm 3: 4 mg
		Arm4: Pamidronate	Arm4: 73	Arm4: 58	Arm 4: 90 mg I.V
(Body et al., 2003)	2003	Arm1: Placebo	Arm1: 158	Arm1: 53 (27-82)	Arm 2: 2 mg
		Arm2: Ibandronate	Arm2: 154	Arm2: 55 (32-77)	Arm 3: 6 mg
		Arm3: Ibandronate	Arm3: 154	Arm3: 57 (34-97)	
(Body et al., 2004)	2004	Arm1: Ibandronate	Arm1: 287	Arm1:57 (27-92)	50 mg orally
		Arm2: Placebo	Arm2: 277	Arm2: 56 (26-87)	
(Tripathy et al., 2004)	2004	Arm1: Placebo	Arm1: 143	Arm1:57 (31-83)	Arm 2: 20 mg
		Arm2: Ibandronate	Arm2: 144	Arm2: 56 (30-82)	Arm 3: 50 mg orally
		Arm3: Ibandronate	Arm3: 148	Arm3: 57 (29-92)	
(Kohno et al., 2005)	2005	Arm1: Zoledronic acid	Arm1: 114	Arm1: 54	4 mg orally
		Arm2: Placebo	Arm2: 113	Arm2: 53	
(Lipton et al., 2008)	2008	Arm1: Intravenous Bisphos- phonate	Arm1: 43	Arm1: 52	Arm 1: IV BP (NA)
		Arm2: Denosumab pooled	Arm2: 211	Arm2: 58	Arm 2: 30-180 mg
(Heras et al., 2009)	2009	Arm1: Ibandronate	150	Arm1: NA	6 gm I.V.
		Arm2: Placebo	(Arm1 + Arm2)	Arm2: NA	
(Fizazi et al., 2009)	2009	Arm1: Intravenous Bisphos-phonate	Arm1: 37	Arm1: 61	Arm 2: 180 mg
		Arm2: Denosumab	Arm2: 74	Arm2: 63	
(Stopeck et al., 2010)	2010	Arm1: Zoledronic acid	Arm1: 1020	Arm1: 56	Arm 1: 4 mg
		Arm2: Denosumab	Arm2: 1026	Arm2: 57	Arm 2: 120 mg
(Barrett-Lee et al., 2014)	2014	Arm1: Ibandronate	Arm1: 704	Arm1: 61 (52-70)	Arm 1: 50 mg
		Arm2: Zoledronic acid	Arm2: 697	Arm2: 61 (52-69)	Arm 2: 4 mg
(Luedders et al., 2015)	2015	Arm1: Ibandronate	Arm1: 17	Arm1: 62 (44-78)	Arm 1: 6 mg
		Arm2: Zoledronic acid	Arm2: 17	Arm2: 55 (31-73)	Arm 2: 4 mg

NA = Not available, I.V. = Intravenous. For each bone-modifying agent results were pooled regardless of dosages or presentation of application such as intravenous or oral administration and merged prior to analysis.

1999; Barrett-Lee et al., 2014; Conte et al., 1996). None of the studies reported a significant difference between directly compared treatment options. As shown in Table 2, results are displayed for every study reporting overall survival. No data was pooled for this outcome because of the heterogeneous presentation of results and effect sizes which were not comparable.

3.4.2. Quality of life

Although quality of life was recorded in seven of the included studies, no overall statement was possible due to the different methods of measurement used (e.g. the Spitzer Quality of Life Index, the EORTC QLQ-C30 Questionnaire, the FACT-G or a specific instrument developed for the study) as well as different measuring time points.

3.4.3. Pain

An evaluation of this outcome across the studies was not possible for the same reasons stated for quality of life, although pain response was reported in 11 studies. Different instruments and scales like the Visual Analog Scale, the Brief Pain Inventory, the Scott Huskisson Scale, or a 4 or 5-step scale were used to assess pain. Since these assessments occurred at different time points per study, results were not comparable.

3.4.4. Skeletal-related events

For SREs, we were able to include seven studies in a network (Fig. 4). Another study investigating clodronate versus no treatment was not linked to this network and was therefore not included, which can also be seen in Fig. 4. As the network meta-analysis in Fig. 5 shows, all three denosumab (RR: 0.62; 95% CI: 0.50 to 0.76), zoledronic acid (RR: 0.72; 95% CI: 0.61 to 0.84) and pamidronate (RR: 0.76; 95% CI: 0.67 to 0.85) were significantly superior to placebo in the random-effects model. *P*-scores show denosumab as the optimal option regarding SRE, followed by zoledronic acid and pamidronate (Fig. 5A). The *P*-scores are based solely on the point estimates and standard errors of the network estimates and measure the degree of certainty that one treatment is better than another treatment, averaged over all competing treatments (Rücker and Schwarzer, 2015; Rücker, 2012b). The *P*-score of the treatment can be interpreted as the median degree of certainty that one treatment is better than the other. Fig. 5B shows results of

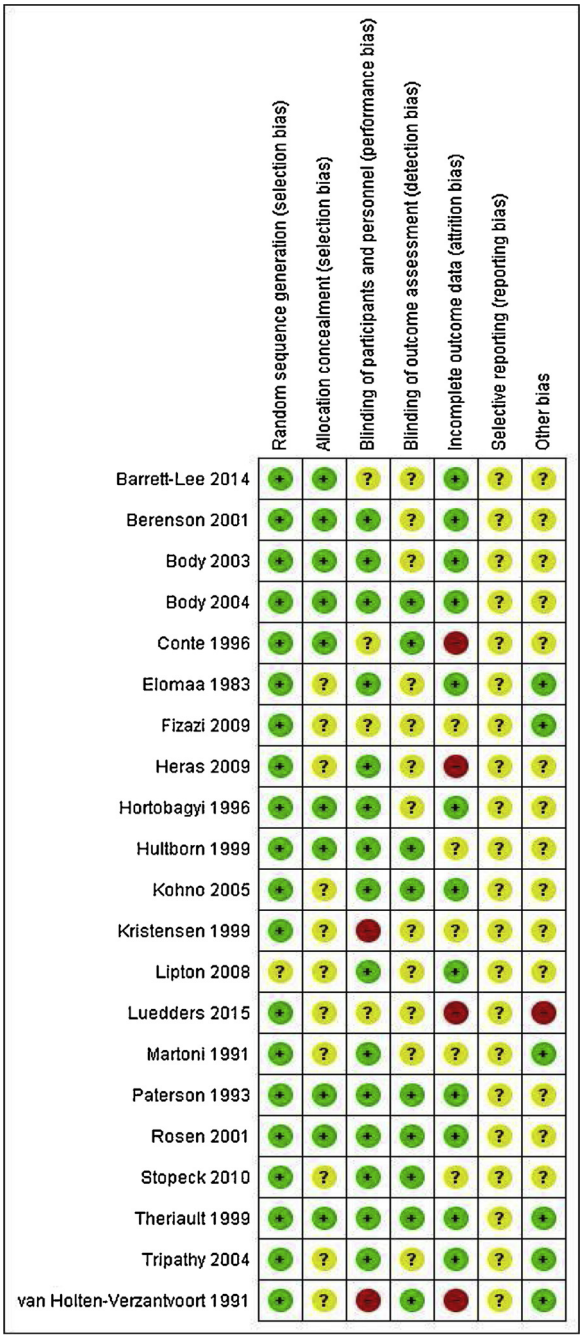

Fig. 2. Risk of bias.

+ = low RoB;? = unclear RoB; - = high RoB

meta-analysis from direct comparisons for SREs.

Looking in detail into specific SREs, pamidronate was superior over clodronate in reducing hypercalcemia in patients receiving the treatments (Suppl. Fig. 1b). Ibandronate was best option in reducing spinal cord compression (Suppl. Fig. 2b) but in respect to pathological fractures and radiotherapy, denosumab treatment was once again superior when compared to zoledronic acid, ibandronate, pamidronate or clodronate (Suppl. Fig 3b & 4b). However the findings are not statistically significant due to the confidence interval overlaps.

As the number of eligible RCTs was too small to yield reliable results we did not perform small study effects assessment using tests for funnel plot asymmetry. Also analysis of subgroups and sensitivity analysis were not conducted since too few studies were found to yield reliable results.

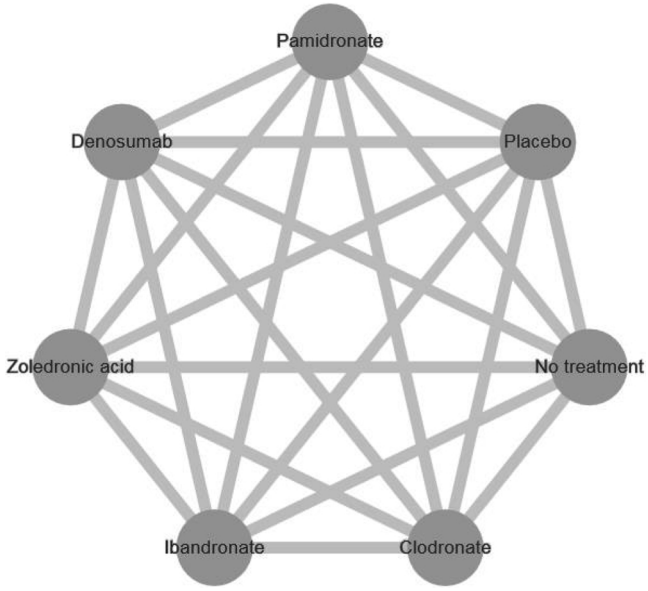

Fig. 3. Ideal network of direct and indirect comparisons. This ideal network shows all direct and indirect comparisons possible between the different treatment options with bisphosphonates (pamidronate, clodronate, ibandronate, zoledronic acid) and the RANK-L inhibitor denosumab compared with placebo or no treatment. Due to limited number of studies and comparisons, it was in some cases not possible to calculate a network meta-analysis for outcomes (overall survival, quality of life, adverse events) or the network was missing a connection (skeletal-related events, see Fig. 4).

3.4.5. Adverse events

Data on adverse events were available from various studies. Some studies reported serious adverse events, other renal complications or osteonecrosis of the jawbone and others grade 3 and / or grade 4 adverse events. The different reporting of adverse events made an overall network meta-analysis impossible. For an overview of reported adverse events see Table 3. In summary, significant adverse events appear to be uncommon, with the risk of osteonecrosis of the jaw for example likely being about 1% for zoledronic acid and about 2% for denosumab.

4. Discussion

In this systematic review and network meta-analysis we compared different available bone-modifying agents given as palliative treatment for breast cancer patients with bone metastases. Our present results demonstrate that all treatments with denosumab, pamidronate and zoledronic acid were significantly superior to placebo treatment regarding reduction of SREs. We found treatment with denosumab to be the first optimal treatment option in reducing SREs followed by zoledronic acid and pamidronate treatment on the basis of P-scores. Our findings are in agreement with Wang et al. who also ranked denosumab superior in reducing SREs in their systematic review which compared different bone targeting agents for prevention of SREs in cancer patients with bone metastases (Wang et al., 2015).

SREs are a main cause of pain and significantly affect the quality of life of patients. And since current available treatments are only of palliative nature, we tried to asses both quality of life and pain response of patients as secondary outcomes in our network meta-analysis. However, due to the numerous different methods of measurement reported by the studies and the discrepancies on the time points taken to measure the outcomes, evaluation across studies was not possible. The lack of homogeneously reported outcome data was also prevalent when trying to analyze overall survival of patients. This is an important finding as it highlights the lack of systemic and consistent reporting of patient relevant outcomes such as quality of life, pain response or

Table 2
Overview of reporting on overall survival.

Reference	Arm 1 Arm 2	*N* of patients	*N* of events	Median OS (months)	*P*-value (arm 1 vs. arm 2)	HR with 95%CI
(Elomaa et al., 1988)	Clodronate	17	6*	NA	< 0.004	NA
	Placebo	17	13*	NA		NA
(van Holten-Verzantvoort et al., 1991)	Pamidronate	81	NA	25	0.98	NA
	No treatment	80	NA	24		
(Hortobagyi et al., 1996)	Pamidronate	185	NA	14,8 (12.6 to 19.9)	0.82	NA
	Placebo	195	NA	14.0 (11.7 to 17.2)		
(Kristensen et al., 1999)	Clodronate	49	24	18.3 (16.3 to 20.3)	0.97	NA
	No treatment	51	25	18.0 (15.7 to 20.2)		
(Theriault et al., 1999)	Pamidronate	182	NA	23.2 (19.3 to 25.8)	0.685	NA
	Placebo	189	NA	23.5 (18.7 to 27.4)		
(Body et al., 2003)	Placebo	158	25	26.7 (in weeks: 106.7 (95 to 124))	NA	NA
	Ibandronate	308	39	in weeks: 116.4 (104 to 133) / 113.3 (97 to 129)		
(Tripathy et al., 2004)	Placebo	143	16	NA	NA	NA
	Ibandronate	292	49	NA		
(Stopeck et al., 2010)	Zoledronic acid	1020	NA	NA	/	0,95 (95% CI 0,81 to 1,11; *p*-value = 0,49)
	Denosumab	1026	NA	NA		
(Barrett-Lee et al., 2014)	Ibandronate	704	436	27,8 (in weeks: 111.3 (103.4 to 118.4)	/	1,086 (95% CI 0,948 to 1,245, *p*-value = 0,24)
	Zoledronic acid	697	395	28,4 (in weeks: 113.4 (103.6 to 124.1)		
(Conte et al., 1996)	Pamidronate	143	7	20	NA	NA
	No treatment	152	18	21.4		

N = number; OS = overall survival; NA = not available; HR = hazard ratio; CI = confidence interval; * = after 24 months.

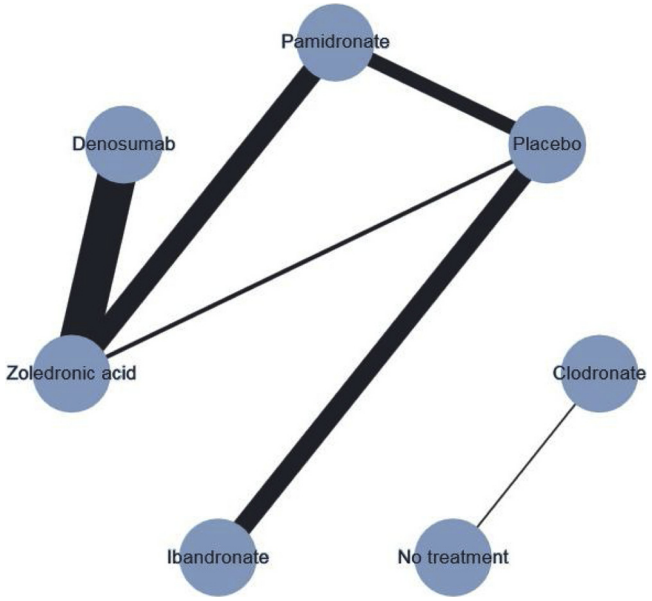

Fig. 4. Network of all treatment options of studies reporting skeletal-related events (SREs). Width of the lines represents proportionality to the number of patients in the comparison. Since two subnetworks were not connected, clodronate could not be considered in the overall analysis.

overall survival in RCTs.

Despite the lack of homogeneous data, we were still able to take advantage of the merits of a network meta-analysis which makes the establishment of a global estimate of treatments for a given set of interventions possible, when pairwise comparisons are not possible due to missing evidence. Network meta-analysis utilizes both direct and indirect effects originating from various sets of evidence and incorporates valid statistical inference methods to rank the interventions and identify the best or worst. Network meta-analysis overcomes the main limitation of meta-analysis which is only capable of evaluating pairwise comparison of treatments, hence limiting its use to head-to-head comparisons which are either not always available in the literature or insufficient to provide evidence based clinical proof (Greco et al., 2013). With this network meta-analysis, we were able to establish a hierarchy of treatment options regarding SREs, which is useful for patients and physicians when making clinical therapy decisions (Greco et al., 2016).

The sensitive, highly complex search strategy we implemented was able to identify references highly specific to breast cancer patients with bone metastasis. Since all studies included were either of low or moderate risk of bias this further validated our findings.

As mentioned in our results, data heterogeneity of reported outcomes prevented us from performing analysis for most of the patient relevant outcomes, even though we already pooled the results of bone-modifying agents regardless of dosages or presentation of application (intravenous or oral). If we had not done this, an overall analysis would have been even more critical.

The process of identifying a suitable measure of a clinical outcome considers various aspects of the nature of the disease or conditions defined in the study, in combination with sources of information by which the required outcome information can be feasibly and reliably obtained (Velentgas et al., 2013). When many clinical aspects are of interest, selecting the clinical outcome measure can be challenging. This challenge was highlighted in a study performed by Harrington et al. which after a comprehensive review of breast cancer literature identified 23 different measures of pain outcome out of which eight measures were given the highest rating and recommended for clinical use (Harrington et al., 2014). This gives physicians a wide range in choosing the outcome measurement tool they would implement in their study resulting in data heterogeneity which prevents the possibility of pooling data for direct and indirect comparisons. We have found this phenomenon to be the bottleneck of network meta-analysis and our study strongly stresses on the need of formulating clinical studies more precisely and establishing a standardised reporting scheme which can be implemented in RCTs. As every NMA our analysis itself comes with strengths and weaknesses. The strength of our analysis is that we were able to compare treatment options indirectly for which no direct evidence is available. An indirect estimate is calculated using estimates from direct meta-analyses, so the within-trial randomization is preserved. Nevertheless, indirect comparison and consequently network meta-analysis provide observational evidence in that the treatments

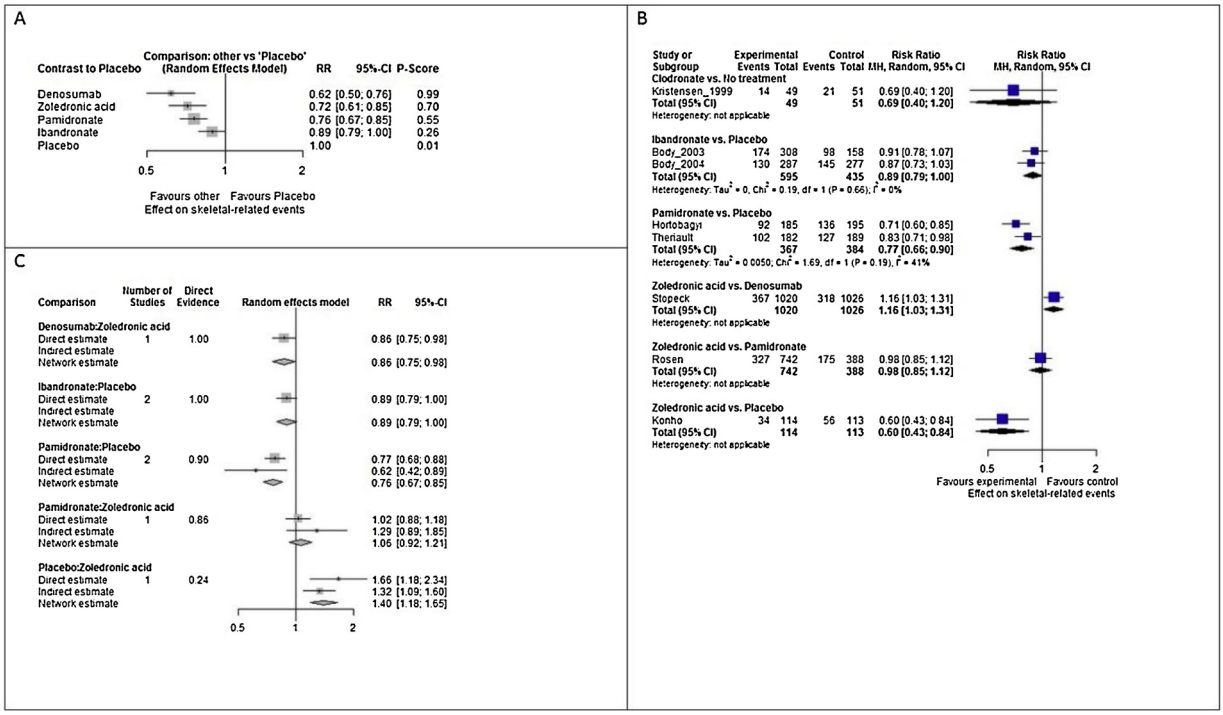

Fig. 5. Network meta-analysis of the pooled data of four different bone-modifying agents compared to each other and placebo of studies reporting skeletal-related events (SREs). (A) Treatment ranking through *P*-scores. Denosumab (RR: 0.62; 95% CI: 0.50 to 0.76), zoledronic acid (RR: 0.72; 95% CI: 0.61 to 0.84) and pamidronate (RR: 0.76; 95% CI: 0.67 to 0.85) were significantly superior to placebo. The *P*-score of the treatment can be interpreted as the median degree of certainty that one treatment is better than another. (B) Meta-analysis of direct comparisons for SREs. (C) Analysis of differences between direct and indirect comparisons regarding the network meta-analysis on SREs.

Table 3
Overview of reported adverse events.

Adverse Events	Treatment 1 Number of events (Number of patients)	Treatment 2 Number of events (Number of patients)	Reference
Renal complications	Ibandronate 15 (287)	Placebo 13 (277)	(Body et al., 2004)
	Zoledronic acid 0 (114)	Placebo 1 (113)	(Kohno et al., 2005)
	Zoledronic acid 86 (1013)	Denosumab 50 (1020)	(Stopeck et al., 2010)
	Ibandronate 172 (704)	Zoledronic acid 226 (697)	(Barrett-Lee et al., 2014)
Osteonecrosis of the jaw	Zoledronic acid 14 (1013)	Denosumab 20 (1020)	(Stopeck et al., 2010)
	Ibandronate 5 (704)	Zoledronic acid 9 (697)	(Barrett-Lee et al., 2014)
Hypocalcaemia	Pamidronate 3 (182)	Placebo 3 (189)	(Theriault et al., 1999)
	Zoledronic acid 1 (114)	Placebo 1 (113)	(Kohno et al., 2005)
	Zoledronic acid 34 (1013)	Denosumab 56 (1020)	(Stopeck et al., 2010)
	Ibandronate 80 (704)	Zoledronic acid 77 (697)	(Barrett-Lee et al., 2014)

being compared have not been randomized directly within the individual trials (Cipriani et al., 2013). This is judged as a weakness of the method and needs to be taken into consideration when interpreting the results.

To conclude, the ranking of different treatment options with bisphosphonates and RANK-L inhibitors was not conclusively clarified from the network meta-analysis performed. However, we were able to establish a treatment hierarchy regarding SREs, denosumab being the best option, followed by zoledronic acid and pamidronate treatments. However, since the analysis was only possible for this one outcome the results cannot be taken to inform clinical decision making per se. The influence of treatments with bisphosphonates or RANK-L inhibitors on quality of life, metastatic pain, overall survival and adverse events are lacking in studies that standardised the reporting of these outcomes. Denosumab might be the best option for the prevention of SREs, but it is considered to cause more critical adverse events like osteonecrosis of the jaw, which needs to be taken into consideration when deciding which treatment option is best for each patient. The results of the present project can therefore be used to formulate clinical studies more precisely in order to standardise outcome reporting and to plan clinical trials optimally and in the interest of patients.

Declarations of interest

None.

Conflict of interest

Yonas Mehari Tesfamariam: none known.
Tina Jakob: none known.
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