Should de-escalation of bone-targeting agents be standard of care for patients with bone metastases from breast cancer? A systematic review and meta-analysis

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Received 6 May 2015; revised 22 June 2015; accepted 24 June 2015

Background: De-escalation of bone-targeted agents, such as bisphosphonates and denosumab, from 4- to 12-weekly dosing is an increasingly used strategy in patients with bone metastases from breast cancer. It is unclear whether there is sufficient evidence to support de-escalation as a standard of care.

Methods: A systematic review of randomized trials comparing standard 4-weekly administration of bone-targeted agents with de-escalated (Q12-weekly) dosing in breast cancer patients was carried out. Medline, PubMed and the Cochrane Register of Controlled Trials were searched from inception until November 2014 for relevant studies. Outcomes of interest included skeletal-related event (SRE) rates, bone pain, adverse events (AEs) and bone turnover biomarkers. Random-effects meta-analyses were carried out.

Results: A total of nine citations representing seven unique studies were eligible. One study is ongoing with no reported data. Six studies reported data for at least one outcome of interest. Data were available comparing standard versus de-escalated therapy for pamidronate (1 study, 38 patients), zoledronate (3 studies, 1117 patients) and denosumab (2 studies, 284 patients). Meta-analysis of five trials reporting data for on-study SRE rates between standard (61/443 patients) and de-escalated (49/392 patients) arms produced a summary risk ratio of 0.90 (95% confidence interval 0.63–1.29). Meta-analyses of data for AEs and bone turnover biomarkers also showed no statistically significant differences between standard and de-escalated arms, though only limited numbers of patients and events were present for most analyses.

Conclusion: In this systematic review of studies of bisphosphonates and denosumab, there appears to be no difference in SREs or pain with de-escalated therapy. While a large, hopefully definitive study is ongoing, the data presented so far are consistent with de-escalation of bone-targeting agents becoming a standard of care for patients with bone metastases from breast cancer.

Key words: bisphosphonate, breast cancer, bone metastasis, skeletal-related event, biomarker, de-escalated treatment

introduction

Bone metastasis is common in breast cancer patients and as a result of increased osteoclast activity and bone destruction, can lead to pain, impaired quality of life and skeletal-related events (SREs), such as pathological fractures, radiotherapy/surgery to bone, spinal cord compression and hypercalcaemia [1–3]. Osteoclast inhibitors, such as bisphosphonates and denosumab, reduce both the frequency of SREs and the time-to-first SRE [4–6]. However, despite their widespread use, SREs remain common [7, 8] and questions around their optimal use remain [9].

Traditionally, bone-targeted agents are given every 3–4 weeks from the time of diagnosis of bone metastasis until death [10]. This dosing schedule was developed from studies in patients with hypercalcaemia and co-administration with standard anticancer agents. However, these schedules ignore the long half-life that many of these agents have in bone [11] as well as the bone biomarker studies (a surrogate marker of SRE risk) [12] which have consistently shown rapid falls in biomarker levels sustained at significantly lower doses, and for longer durations than 3–4 weeks, for both bisphosphonates [13, 14] and denosumab [15]. Given concerns regarding the toxicity of these agents [16], there has been increasing interest from oncologists [10] and patients [13] in finding the optimal dosing interval [9, 17].

If de-escalation of treatment is as efficacious as 3–4 weekly dosing, it could reduce clinic visits, drug side-effects for patients,
in addition to reducing costs to both the patient and the health care system. A previous systematic review showed that a number of studies have explored de-escalation of bone-targeted agents [18]. As there is now more data available, a systematic review and meta-analysis was carried out in order to assess whether or not de-escalation should be considered standard of care in patients with bone metastases from breast cancer.

**methods**

**research question and eligibility criteria**

The literature search of an existing systematic review covering publications between 1946 to February 2013 [18, 19]. Additional data have been presented since that time and, therefore, the current systematic review extended the coverage of the literature search from March 2013 until November 2014. The research question was phrased in the Population-Intervention-Comparator-Outcomes-Study design framework as: ‘Does administration of bone-targeted agents every 12 weeks, to breast cancer patients with bone metastases, provide similar benefit and fewer harms compared with 3–4 weekly (Q3–4w) administration?’ Studies were eligible if they were randomized, included patients with breast cancer, and involved treatment with any bone-targeted agent. No additional criteria related to duration and dose of bone-targeting agent used before study enrolment was specified. The clinical outcomes of interest were SREs, bone pain (measured by a validated scale), quality of life (measured by a validated scale), adverse events (AEs; renal outcomes, osteonecrosis of the jaw (ONJ), bone pain, hypocalcaemia) and reduction in bone turnover biomarkers [urinary N-terminal telopeptide (NTx), serum C-terminal telopeptide (CTx)]. The comparator was standard 3–4 weekly treatment with the same bone-targeted agent as in the de-escalated arm.

**literature search to identify studies**

An electronic literature search was designed for our original review [18] by an information specialist to identify potentially eligible citations from: Ovid Medline (-present), PubMed (for non-Medline records) and Cochrane Register of Controlled Trials. The search was peer-reviewed by a second librarian according to PRESS criteria [20]. The search strategy for Ovid Medline(R) is provided in supplementary Appendix S1, available at Annals of Oncology online. Conference abstracts for three major oncology meetings (American Society of Clinical Oncology, European Society for Medical Oncology and San Antonio Breast Cancer Symposium) from 2013 to 2014 were also searched (supplementary Appendix S2, available at Annals of Oncology online).

**study selection**

Stage 1 review consisted of screening of all titles and abstracts by two independent reviewers to identify a set of potentially relevant citations. Full-text articles of the citations identified in

![Figure 1. Flow diagram of study selection process.](https://academic.oup.com/annonc/article-abstract/26/11/2205/263080)
<table>
<thead>
<tr>
<th>Author (reference); year</th>
<th>Industry funded?</th>
<th>Study design information</th>
<th>Sample size</th>
<th>Mean age (years)</th>
<th>Patient inclusion criteria</th>
<th>Relevant patient demographics</th>
<th>Outcomes assessed</th>
<th>Duration</th>
<th>Study status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate</td>
<td></td>
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<tr>
<td>Amir et al. (Reform) [28]; 2013</td>
<td>No</td>
<td>Pilot, feasibility study randomized, Q4 weekly versus Q12 weekly</td>
<td>38</td>
<td>Q3–4w: 50 Q12w: 60</td>
<td>MBC (Bone Mets) baseline serum CTx &lt;600 ng/l</td>
<td>≥3 months of prior BP use</td>
<td>CTx, pain (FACT-BP, BPI), SREs, pain medication, BAP</td>
<td>1 year</td>
<td>Complete—peer-reviewed publication</td>
</tr>
<tr>
<td>Kuchuk et al. [23]; 2013</td>
<td>No</td>
<td>Q4 weekly versus Q12 weekly. Updated from randomized non-inferiority feasibility trial [27]</td>
<td>38</td>
<td>NR</td>
<td>MBC (Bone Mets) baseline serum CTx &lt;600 ng/l</td>
<td>≥3 months of prior BP use</td>
<td>Correlation between CTx/ BAP and pain scores (FACT-BP/BPI)</td>
<td>1 year</td>
<td>Complete—peer-reviewed publication</td>
</tr>
<tr>
<td>Addison et al. [26]; 2014</td>
<td>No</td>
<td>Pilot, randomized trial (data from pilot, feasibility, randomized trial [27])</td>
<td>30</td>
<td>NR</td>
<td>MBC (Bone Mets) baseline serum CTx &lt;600 ng/l</td>
<td>≥3 months of prior BP use</td>
<td>CTx, NTx, pain (FACT-BP, BPI), SREs, BSAP, BSP</td>
<td>1 year</td>
<td>Complete—peer-reviewed publication</td>
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<tr>
<td>Zoledronate</td>
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<tr>
<td>Amadori et al. [27]; 2013</td>
<td>Yes</td>
<td>Open label, randomized Q4 weekly versus Q12 weekly</td>
<td>425</td>
<td>Q4w: 59.8 (median) Q12w: 60.4 (median)</td>
<td>MBC (Bone Mets)</td>
<td>9–12 months of prior zoledronate</td>
<td>SMR; number of SREs/patient/year, time-to-first SRE, bone pain, bone marker (N-telopeptide of type I collagen; NTX) levels, and safety</td>
<td>1 year</td>
<td>Complete—peer-reviewed publication</td>
</tr>
<tr>
<td>Hortobagyi et al. (OPTIMIZE-2) [24]; 2014</td>
<td>Yes</td>
<td>Randomized, double blind, Q4 weekly versus Q12 weekly</td>
<td>403</td>
<td>Q4w: 59.2 Q12w: 58.6</td>
<td>MBC (Bone Mets)</td>
<td>Previously received &gt;9 doses of monthly BP</td>
<td>Bone turnover marker urine NTX corrected for urine creatinine level, and SREs</td>
<td>1 year</td>
<td>Complete—abstract presentation</td>
</tr>
<tr>
<td>Coleman et al. (BISMARK) [29]; 2012</td>
<td>Yes</td>
<td>Open label, randomized S-ZOL 3–4w or M-ZOL (15–16w; 8–9w or 3–4w) if urine NTX levels were &lt;50, 50–100, &lt;100 nmol/mmol creatinine</td>
<td>289</td>
<td>MBC (Bone Mets)</td>
<td>No prior BP</td>
<td>Bone turnover marker urine NTX corrected for urine creatinine level, and SREs</td>
<td>2 years</td>
<td>Completed 2-year follow-up despite early closure. Abstract presentation</td>
<td></td>
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<tr>
<td>Denosumab</td>
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<tr>
<td>Lipton et al. [30]; 2007</td>
<td>Yes</td>
<td>Randomized, blinded study of five denosumab regimens (4w 30 mg, 120 or 180 mg; or 12w 60 or 180 mg) and an i.v. BP regimen (4w use of physician’s choice)</td>
<td>255</td>
<td>180 mg Q4w: 57.6 Q12w 180 mg: 58.2</td>
<td>MBC (Bone Mets)</td>
<td>No prior i.v. BP</td>
<td>Bone turnover marker urine N-telopeptide corrected for urine creatinine level, and SREs; safety</td>
<td>13 weeks for biomarkers</td>
<td>Complete—peer-reviewed publication</td>
</tr>
</tbody>
</table>

*Continued*
Table 1. Continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Industry funded?</th>
<th>Study design information</th>
<th>Sample size</th>
<th>Mean age (years)</th>
<th>Patient eligibility criteria</th>
<th>Relevant patient demographics</th>
<th>Outcomes assessed</th>
<th>Duration</th>
<th>Study status</th>
<th>Open—abstract presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fizazi et al. [15]</td>
<td>Yes</td>
<td>Randomized open-label study: three arms of 4 weekly BP, denosumab 180 mg Q12w or zoledronate 180 mg Q12w</td>
<td>74 patients</td>
<td>Q12w–66</td>
<td>Histologically confirmed carcinoma, excluding patients with prior multiple myeloma or bone metastases, ECOG 0–1</td>
<td>Bone metastases from breast or prostate cancer</td>
<td>SRE, safety, time to SSE, quality of life, health economic, bone turnover markers</td>
<td>15 months</td>
<td>Complete—peer-reviewed publication</td>
<td></td>
</tr>
<tr>
<td>Templeton et al. [25]</td>
<td>No</td>
<td>Open-label randomized phase III non-inferiority trial: denosumab 120 mg S/C Q12 weekly versus Q4 weekly standard treatment arm (Q4w)</td>
<td>1380 patients</td>
<td>1380</td>
<td>Bone metastases from breast cancer, except lung, or multiple myeloma, or castration-resistant prostate cancer</td>
<td>Time to first symptomatic skeletal event (SSE), quality of life, health economic, bone turnover markers</td>
<td>SRE, safety, time to SSE</td>
<td>13 months</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td>Hortobagyi et al. [18]</td>
<td>Yes</td>
<td>Open-label randomized trial: zoledronate 4 mg Q4w versus placebo</td>
<td>304 patients</td>
<td>74</td>
<td>No prior BP</td>
<td>Bone metastases from breast cancer, except lung, or multiple myeloma, or castration-resistant prostate cancer</td>
<td>SRE, quality of life</td>
<td>13 months</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td>Fizazi et al. [15]</td>
<td>Yes</td>
<td>Randomized open-label study: three arms of 4 weekly BP, denosumab 180 mg Q12w or zoledronate 180 mg Q12w</td>
<td>72 patients</td>
<td>Q12w–66</td>
<td>Histologically confirmed carcinoma, excluding patients with prior multiple myeloma or bone metastases, ECOG 0–1</td>
<td>Bone metastases from breast or prostate cancer</td>
<td>SRE, safety, time to SSE, quality of life, health economic, bone turnover markers</td>
<td>15 months</td>
<td>Complete—peer-reviewed publication</td>
<td></td>
</tr>
<tr>
<td>Templeton et al. [25]</td>
<td>No</td>
<td>Open-label randomized phase III non-inferiority trial: denosumab 120 mg S/C Q12 weekly versus Q4 weekly standard treatment arm (Q4w)</td>
<td>1380 patients</td>
<td>1380</td>
<td>Bone metastases from breast cancer, except lung, or multiple myeloma, or castration-resistant prostate cancer</td>
<td>Time to first symptomatic skeletal event (SSE), quality of life, health economic, bone turnover markers</td>
<td>SRE, safety, time to SSE</td>
<td>13 months</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td>Hortobagyi et al. [18]</td>
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<td>SRE, quality of life</td>
<td>13 months</td>
<td>Complete</td>
<td></td>
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</table>

Stage 1 screening were then screened in stage 2, again by two independent reviewers. RCTs included in the previous systematic review were also re-screened. At both stages, any discrepancies were resolved by discussion, with consultation of a third party if required. The process of study selection was documented using a flow diagram as recommended by the PRISMA statement [21] (supplementary Appendix S3, available at Annals of Oncology online).

**Data collection and risk of bias assessment**

Data collection was carried out by two reviewers using a standardized data collection form. This form gathered information from each study in terms of publication characteristics, patient eligibility criteria and demographics, intervention details (including type of bone-targeting agent used and frequency thereof) and outcome data as mentioned earlier. Studies were independently assessed for risk of bias by two reviewers (MFKI, CJ) using the Cochrane Collaboration’s risk of bias tool for randomized trials [22]. Discrepancies in data collection were resolved by discussion among the reviewers. When selected citations were not available as peer-reviewed manuscripts, the abstracts were used for data extraction (but were not assessed for risk of bias). Funding for the study was from internal sources, there was no pharmaceutical company funding.

**Data analysis**

If studies were judged sufficiently homogeneous, in terms of patient characteristics and study design, we planned to use random-effects meta-analysis to synthesize outcome data. Continuous outcome measures were summarized as weighted mean differences while binary outcomes were synthesized using odds ratios, and all summary estimates were reported with point estimates and corresponding 95% confidence intervals (CIs). Findings were presented using forest plots which also included study-level effect estimates to enable inspection of variability in findings from study to study for each outcome. Statistical heterogeneity was assessed using the Cochrane Q statistic and the I² statistic [23]. The standard treatment arm (Q4w) was used as the reference treatment of all meta-analyses. Where data were not considered amenable to meta-analysis based on study characteristics, a narrative approach to summary of study-specific results was employed.

**Results**

**Quantity of evidence identified**

The electronic literature search identified 158 unique citations from March 2013 to November 2014 following removal of duplicate citations, and the five studies included in the 2013 review were also screened again. Stage 1 screening identified five potentially eligible new citations for full-text review along with the existing collection of studies. At stage 2 screening, all five of the new citations were found to meet the pre-specified eligibility criteria [15, 24–27], two of which were published as meeting abstracts (Hortobagyi’s OPTIMIZE-2 study [25] and Templeton’s REDUSE study [26]). A total of five new trials consisting of 904 patients were included, in addition to four studies [28–30] from the previous review [18, 19]. One study [31] included in the
previous review was excluded from this update, as it focused upon zoledronate dose rather than dose frequency. One trial [26] is ongoing with no available outcome data.

Figure 1 shows an overview of the study selection process, while supplementary Appendix S4, available at *Annals of Oncology* online, lists included and excluded studies after full-text screening. A total of nine manuscripts, representing seven unique trials, were included. An overview of their characteristics is provided in Table 1. Detailed narrative summaries of each of the included studies have is provided in supplementary Appendix S5, available at *Annals of Oncology* online.

**study characteristics**

Three studies (OPTIMIZE-2 [25] REDUSE [26] and BISMARK [30]) selected for inclusion were available as abstracts with limited study data. Characteristics of the studies are described in Table 1. One study was published in 2007 [30], one in 2009 [15], one in 2012 [30], three in 2013 [24, 28, 29] and three in 2014 [25–27]. Among the studies, five were funded by industry [15, 25, 28, 30], two were internally funded [24, 29], one biomarker substudy was funded by a peer-reviewed grant [27] and one was funded by the national health insurance provider [26]. The number of enrolled patients ranged from 30 [27] to 425 [28]. The study durations varied between 13 weeks and 2 years [30]. Four studies were open labelled [15, 28–30], two were internally funded [24, 29], one study was double blind for the denosumab arms [30] and one was initially double blind but subsequently unblinded to enhance accrual [25]. Three studies were pilot feasibility studies [24, 27, 29]. One study evaluated de-escalation with pamidronate [29], three with zoledronate [25, 28, 29] and two with denosumab [15, 30].

Four full-text articles were available for risk of bias assessment [15, 28, 29, 30] (supplementary Appendix S6, available at *Annals of Oncology* online). Two studies were excluded from bias assessment as the study used the same randomized trial data as one of the included studies [24]. Two studies were excluded, as they were available in abstract form only [25, 30]. One study [29] was judged to have high risk of bias in the domain of outcome assessment, while one other [30] had high risk of bias in regard to blinding of participants and personnel.

**patient characteristics**

All studies enrolled patients with metastatic breast cancer with bone involvement, while another included patients with a range of malignancies [15] and one ongoing study also includes patients with prostate cancer [26]. For the study with mixed tumour types, as much breast cancer-specific data as possible was extracted from the corresponding manuscript (and subsequent update [32] and from www.clinicaltrials.gov). Prior treatment with bisphosphonates before randomization was an inclusion criterion in five studies [15, 24, 25, 28, 29] and an exclusion criterion in three [26, 30].

**findings**

**skeletal-related events**: Studies reported a number of SRE-related outcomes including SRE rates (proportion of patients experiencing at least one on study SRE) (six studies), time-to-first on-study SRE (one study) and skeletal morbidity rates (SMRs) (three studies). As there was available data for the number of patients experiencing on-study SREs available from five trials, meta-analysis of this outcome was carried out. Data for on-study SRE rates for both bisphosphonates and denosumab between standard (87/510 SREs) and de-escalated (88/510 SREs) arms produced a summary risk ratio (RR) of 0.90 (95% CI 0.63–1.29) (Figure 2). Statistical heterogeneity, as measured by $I^2$, was low (0%).

For the three studies reporting SMRs with zoledronate, the mean SMRs were 0.22 (95% CI 0.14–0.29) and 0.26 (95% CI 0.15–0.37) for ZOOM and 0.46 (SD 1.063) and 0.50 (SD 1.500) for OPTIMIZE-2 for standard versus de-escalated treatment, respectively. Coleman et al. reported SMRs of 0.52 (90% CI 0.47–0.58) and 0.72 (90% CI 0.67–0.77) for the standard and
Table 2. Meta-analysis results for adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Renal</th>
<th>Bone pain</th>
<th>Hypercalcemia</th>
<th>Osteonecrosis of the jaw</th>
<th>Hypocalcaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiri [28]</td>
<td>Pamidronate</td>
<td>0/19 (0%)</td>
<td>0/10 (0%)</td>
<td>0/19 (0%)</td>
<td>0/19 (0%)</td>
<td>0/19 (0%)</td>
</tr>
<tr>
<td>Amatori [27]</td>
<td>Zoledronate</td>
<td>3/216 (1.4%)</td>
<td>1/203 (0.5%)</td>
<td>2/216 (0.9%)</td>
<td>2/216 (0.9%)</td>
<td>0/216 (0%)</td>
</tr>
<tr>
<td>Hertogheim [24]</td>
<td>Zoledronate</td>
<td>2/200 (1.0%)</td>
<td>1/203 (0.5%)</td>
<td>2/200 (1.0%)</td>
<td>2/200 (1.0%)</td>
<td>0/200 (0%)</td>
</tr>
<tr>
<td>Fizazi [15]</td>
<td>Denosumab</td>
<td>0/38 (0%)</td>
<td>0/36 (0%)</td>
<td>5/38 (13.2%)</td>
<td>3/36 (8.3%)</td>
<td>6/38 (15.8%)</td>
</tr>
<tr>
<td>Lipton [30]</td>
<td>Denosumab</td>
<td>0/43 (0%)</td>
<td>0/43 (0%)</td>
<td>5/43 (11.6%)</td>
<td>3/43 (7.0%)</td>
<td>6/43 (14.0%)</td>
</tr>
<tr>
<td>Aggregate totals</td>
<td></td>
<td>5/516 (1.0%)</td>
<td>4/510 (0.8%)</td>
<td>7/81 (8.6%)</td>
<td>4/79 (5.1%)</td>
<td>20/297 (6.7%)</td>
</tr>
</tbody>
</table>

RR from meta-analysis with 95% CI: 0.83 (0.16–4.42) 0.58 (0.18–1.90) 0.86 (0.46–1.60) 0.86 (0.46–1.62) 0.86 (0.48–1.53) (Table 2 and supplementary Appendix S7a, available at Annals of Oncology online).

For all summary relative risks, the reference treatment is Q4w. Values <1 favour Q12w therapy.

I² measure of heterogeneity: 22% 0% 0% 0% 0%

For on-study SRE (hazard ratio 1.06; 95% CI 0.70–1.60).

**Discussion**

Bone pain: Data using validated measures of bone pain were only available from two studies. The REFORM study reported data using the Brief Pain Inventory (BPI) and Functional Assessment of Cancer Therapy–Bone Pain (FACT-BP) [24, 27, 29]. Trends in pain scores over time for both FACT-BP and BPI did not significantly differ between groups for cumulative scores from baseline to 48 weeks (P = 0.386). The ZOOM study reported that there was no difference between the standard and de-escalated groups in bone pain, as assessed by the Verbal Rating Score for pain on movement or pain at rest at the end of the study [26]. Given the variation in the reporting of pain outcomes, a meta-analysis was not carried out.

Adverse events: A number of different AEs and toxicities were reported. As most studies used different methods of assessment, their findings are presented in supplementary Appendix S5, available at Annals of Oncology online. For the purposes of meta-analysis, data for on-study renal AEs was available from five studies. Comparison of standard (23 events; 21 AEs and 2 SAEs) and de-escalated (20 events; 17 AEs and 3 SAEs) groups using meta-analysis produced a summary risk ratio of 0.86 (95% CI 0.48–1.53) (Table 2 and supplementary Appendix S7a, available at Annals of Oncology online). Statistical heterogeneity as measured by I² was low (0%). For on-study ONJ, data were available from five studies; again, due to the fundamentally different design of the study, data from BISMARK were excluded from the meta-analysis. Comparison of standard (5 events; 2 AEs and 3 SAEs among 600 patients) and de-escalated (4 events, all SAEs among 551 patients) arms produced a summary risk ratio of 0.83 (95% CI 0.16–4.42) (Table 2 and supplementary Appendix S7b, available at Annals of Oncology online). Statistical heterogeneity, as measured by I², was low (22%); it is noted that three of the five studies were excluded from meta-analysis due to the presence of 0 events in both groups.

Data for on-study bone pain, as an AE, were available from three studies. Comparison of standard (30 events) and de-escalated (21 events) arms produced a summary risk ratio of 0.86 (95% CI 0.46–1.62) (Table 2 and supplementary Appendix S7c, available at Annals of Oncology online). Statistical heterogeneity, as measured by I², was low (0%). Finally, due to the
incidence of potentially fatal hypocalcaemia described in the prostate cancer population with denosumab, we evaluated reporting of this AE. Data for on-study hypocalcaemia as an AE were available for three studies. Comparison of standard (7 events) and de-escalated (4 events) arms produced a summary risk ratio of 0.58 (95% CI 0.18–1.90) (Table 2 and supplementary Appendix S7d, available at Annals of Oncology online). Statistical heterogeneity as measured by $I^2$ was low (0%).

**Biomarkers of bone turnover:** Biomarkers of bone turnover such as CTx and NTx have been used in a number of studies as a surrogate marker for risk for mortality and subsequent SRE risk [33, 34]. Five trials reported data on bone turnover biomarkers (Table 3 and supplementary Appendix S7e–f, available at Annals of Oncology online). Individual study data are shown in supplementary Appendix S4, available at Annals of Oncology online. Meta-analysis of both uNTx (Table 3 and supplementary Appendix S7e, available at Annals of Oncology online) and sCTx (Table 3 and supplementary Appendix S7f, available at Annals of Oncology online) showed no statistically significant differences between the standard and de-escalated arms. Statistical heterogeneity, as measured by $I^2$, was low for uNTx (0%) and sCTx (10%).

### Discussion

The increasing interest from oncologists [10] and patients [13] in identifying the optimal dosing interval of bone-targeting agents [9] has been driven mainly by concerns regarding the toxicity of these increasingly potent agents being used for increasingly periods of time [16]. However, if de-escalation of treatment to less frequent dosing is as efficacious as 3–4 weekly dosing, it could not only lessen clinic visits for patients, but could also lead to reduced drug side-effects and costs to both the patient and the health care system.

SREs are the most commonly studied end point for trials of bone-targeting agents. SRE data were available from all included studies either in terms of time-to-first on-study SRE, percentage of patients having an on study SRE, or as the skeletal morbidity rate. The results of the meta-analysis for the number of patients having on study SREs showed no evidence of a difference between the de-escalated and standard arms, with an inconclusive CI and summary estimate near the null (RR 0.99, 95% CI 0.76–1.29). Similarly, another important palliative indication for bone-targeted agents is pain control. Unfortunately, while individual studies reported no difference between arms for pain scores, there were insufficient common data to allow for meta-analysis to be carried out.

Another potential benefit of de-escalation would be for reduction of the frequencies of AEs and toxicity. While the data from individual studies would suggest that standard dosing was associated with increased rates of renal toxicity [25], osteonecrosis of the jaw [30], GI symptoms [28] than de-escalated therapy (Table 2 and supplementary Appendix S7, available at Annals of Oncology online), the variable reporting for different studies in terms of the type of tool used for measuring each type of toxicity placed limitations on meta-analyses. However, it appears that overall, for renal toxicity, osteonecrosis of the jaw, bone pain and hypocalcaemia, there were no statistically significant differences between study arms.

Biomarkers of bone turnover have been used as a surrogate indicator for pain, survival and subsequent SRE risk [35, 36]. There were variations between the studies in terms of which biomarkers were collected, with studies using urinary NTX [13, 26], sCTx [29, 30] or BSAP [30]. Only one study used all three markers [30]. As with the toxicity reporting, the different types of analysis used to define biomarker response placed limitations on meta-analyses. However, the role of biomarkers of bone turnover as a surrogate of subsequent SRE risk, in an era of increasingly effective anti-cancer therapies, is being increasingly questioned [34].

There are a number of limitations to both the studies included in this review and the subsequent meta-analyses. Studies used different agents (pamidronate, zoledronate or denosumab), enrolled patients with different durations of prior bone-targeted agent use (either no prior therapy [26, 30], >3 months [29], >9 months [25] or 9–12 months [28]), and did not always report common clinical end points. Important palliative outcomes including pain and use of analgesia were only available in two studies, and no studies reported on quality of life. Importantly, three studies were only available as meeting abstracts [25, 26, 30]; given this limitation, additional details of interest in terms of study methods, patient flow and observed outcomes were not available, and we could not formally assess these studies for risk of bias. The OPTIMIZE-2 study had a change in trial methodology from double blind to unblinded after commencing as part of a successful attempt to increase accrual. Additionally, one study terminated early due to

### Table 3. Meta-analysis results for uNTx and sCTx

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>uNTx</th>
<th>sCTx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q4w, n/N (%)</td>
<td>Q12w, n/N (%)</td>
<td>Q4w, n/N (%)</td>
</tr>
<tr>
<td>Addison [26]</td>
<td>Pamidronate</td>
<td>10/13 (76.9%)</td>
<td>13/17 (76.5%)</td>
</tr>
<tr>
<td>Amir [28]</td>
<td>Denosumab</td>
<td>36/36 (94.7%)</td>
<td>33/36 (91.7%)</td>
</tr>
<tr>
<td>Fizazi [15]</td>
<td>Denosumab</td>
<td>40/43 (93.0%)</td>
<td>40/43 (93.0%)</td>
</tr>
<tr>
<td>Lipton [30]</td>
<td>Denosumab</td>
<td>86/94</td>
<td>86/96</td>
</tr>
<tr>
<td>Aggregate Totals</td>
<td>RR from meta-analysis with 95% CI</td>
<td>0.99 (0.91–1.07)</td>
<td>0.99 (0.90–1.08)</td>
</tr>
<tr>
<td>$I^2$ measure of heterogeneity</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

For all summary measures, Q4w is the reference treatment. Values <1 favour Q12w therapy. RR, risk ratio.
challenges with enrolment, achieving only 289 of the targeted 1400; as such, it remains unclear whether study findings might have changed with additional recruitment. Despite these limitations, it is of interest to note that there were consistent patterns across all trials, irrespective of the bone-targeted agent under investigation. There was no signal that de-escalation was associated with increased SRE risk or pain.

conclusions

There is increasing interest from patients and physicians about the use of de-escalated bone-targeted therapy. In this systematic review of studies of bisphosphonates and denosumab, there appears to be no difference in SREs or pain with de-escalated therapy. While a large, hopefully definitive study, is ongoing [26], the data presented so far are consistent with de-escalation of bone-targeting agents becoming a standard of care for patients with bone metastases from breast cancer.

disclosure

BH reports personal fees from Amgen Canada, outside the submitted work. All remaining authors have declared no conflicts of interest.

references

Why has active immunotherapy not worked in lung cancer?

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Received 14 October 2014; revised 22 March 2015; accepted 7 July 2015

Vaccines that rely on active specific stimulation of the host immune system have the potential to trigger durable antitumor responses with minimal toxicity. However, in nonsmall-cell lung cancer (NSCLC), several large phase III trials of vaccines reported within the last year have yielded disappointing results. Compared with placebo, belagenpumatucel-L (an allogeneic tumor cell vaccine), tecemotide (a peptide vaccine targeting MUC-1) and melanoma-associated antigen-A3 (a protein-based vaccine) did not improve outcomes in NSCLC. The lack of clinically significant outcomes, despite their ability to prime and expand tumor antigen-specific T cells could at least partly be attributed to the inability of vaccine-induced T-cell responses to overcome the tumoral mechanisms of immune escape which limit the clonal expansion of T cells following vaccination. A number of such mechanisms have been recognized including reduced antigen presentation, antigenic loss, cytokines, immunosuppressive cells and immune checkpoints. Strategies aimed at modulating the immune checkpoints have shown promise and are on the verge of revolutionizing the therapeutic landscape of metastatic NSCLC. Overcoming immune tolerance and improving the activation of antitumor T cells via combinatorial approaches may represent a new and more promising therapeutic application for active immunotherapies in NSCLC.

Key words: active immunotherapy, vaccines, nonsmall-cell lung cancer, immune checkpoint, tumor-mediated immunosuppression

introduction

The significant and durable responses induced by antibodies blocking the programmed cell death-1 (PD-1) checkpoint have led to a renewed interest in immunotherapy for nonsmall-cell lung cancer (NSCLC) [1, 2]. These results are particularly encouraging given the many unsuccessful attempts at immunotherapy in NSCLC over the last several years. In general, these have included active immunotherapies which rely on the ability of the patient’s own immune system to mount an immune response specific to tumor-associated antigens, passive immunotherapy which uses exogenous lymphocytes or antibodies to mediate an immune response and nonspecific immune stimulation which should be effective regardless of the tumor antigen which stimulates the immune response [3, 4].

Active specific stimulation of the host immune system has the potential to cause durable antitumor responses with minimal toxicity. This promise of antigen-specific immunotherapy has borne out in prostate cancer where the use of sipuleucel-T, an autologous active cellular immunotherapy prolonged overall survival (OS) among men with metastatic castration-resistant prostate cancer [5]. However, in NSCLC, several agents whose large phase III trial results have been reported within the last year have yielded no significant benefit. Given the dire need for better therapies and the cost of drug development, it is imperative to try to understand these failures. In this article, we will review the phase III trial results of recently reported antigen-specific immunotherapeutic approaches in NSCLC, explore the potential reasons behind their failure and discuss strategies for the future.

antigen-specific immunotherapeutic approaches in NSCLC

belagenpumatucel-L

Belagenpumatucel-L (Lucanix) is an allogeneic tumor cell vaccine, which consists of four irradiated NSCLC cell lines that...