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Review Article

A systematic review of dosing frequency with bone-targeted agents for patients with bone metastases from breast cancer

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ABSTRACT

Background: Bone-targeted agents are usually administered to breast cancer patients with bone metastases every 3–4 weeks. Less frequent ('de-escalated') treatment may provide similar benefits with improved safety and reduced cost.
Methods: To systematically review randomised trials comparing de-escalated treatment with bone-targeted agents (i.e. every 12–16 weeks) to standard treatment (i.e. every 3–4 weeks), a formal systematic review of the literature was performed. Two individuals independently screened citations and full text articles. Random effects meta-analyses of clinically important outcomes were planned provided homogeneous studies were identified.
Results: Five relevant studies ($n=1287$ patients) were identified. Sample size ranged from 38 to 425. Information on outcomes including occurrence of SREs, bone pain, urinary N-telopeptide concentrations, serum C-telopeptide concentrations, pain medication use and safety outcomes was not consistently available. Two trials were non-inferiority studies, two dose-response evaluations and one was a pilot study. Bone-targeted agents use varied between studies, as did duration of prior therapy. Patient populations were considered heterogeneous in several ways, and thus no meta-analyses were performed. Observations from the included studies suggest there is potential that 3 month de-escalated treatment may provide similar benefits compared to 3–4 weekly treatment and that lower doses of zoledronic acid and denosumab might be equally effective.
Conclusions: Studies comparing standard and de-escalated treatment with bone-targeted agents in breast cancer are rare. The benefits of standard treatment compared to de-escalated therapy on important clinical outcomes remain unclear. Future pragmatic studies must be conducted to determine the merits of this approach.

1. Background

Bone is the most common site of breast cancer recurrence [1]. Patients diagnosed with bone metastases are presently treated with bone-targeting agents, such as bisphosphonates and RANK ligand antibodies, every 3–4 weeks for the remainder of their life [2]. Historically, the frequency of dose administration was developed partly on schedules based on hypercalcaemia trials and limited bone marker studies but also for convenience rather than efficacy and safety purposes, as it allowed investigators to deliver bone-targeted agents at the same time patients were also receiving chemotherapy (i.e. every 3 weeks) or every 4 weeks if the patient was receiving endocrine therapies. However, this rationale ignores the pharmacokinetics of BTAs, which may have a half-life in bone of many years [3,4], and the modest absolute magnitude of benefit of these agents [5].

Despite the widespread use of BTAs, the question around optimal dose and dosing intervals remains unanswered [6–8]. This is particularly important given that drug induced toxicities are directly related to both the potency of the agent and also the cumulative dose received. Indeed, the incidence of BTA-associated osteonecrosis of the jaw is now approaching 10% in some selected chart reviews and online registries, making this by far the most

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common and serious side effect of treatment [9]. A number of reported pilot studies [10–13] have suggested that patients can derive similar palliative benefits from bone-targeted agents when given at less frequent intervals, while others are ongoing [14]. While we have previously used the term de-escalation to imply reduced frequency of administration [11] it can also relate to a reduced dose per unit time. In order to assess the need for further randomized controlled trials of standard 3–4 week treatment with bone-targeted agents in breast cancer patients with metastatic disease compared to de-escalated treatment, we performed a systematic review of the published literature.

2. Methods

2.1. Study question and inclusion criteria

Our systematic review was designed to summarize available information addressing the following research question: "Does de-escalated treatment (i.e. every 3–4 months) with bone-targeted agents in breast cancer patients with metastatic disease provide similar benefit to 3–4 weekly treatment?" The Population–Intervention–Comparator–Outcome–Study Design (PICOS) framework was employed to structure the research question and to design the literature search. The population of interest was breast cancer patients with metastatic disease to bone; the intervention of interest was de-escalated/de-intensified treatment with any bone-targeted agent (denosumab, pamidronate, zoledronate, ibandronate, clodronate), while the comparator was standard 3–4 weekly treatment with any bone-targeted agent. Outcomes of interest included skeletal related events, bone pain, and quality of life, and only randomized controlled trials were considered eligible.

Inclusion criteria used during Stage 1 (i.e. citation review) and Stage 2 (i.e. full text review) screening closely mirrored the above PICOS criteria, with addition details used to determine inclusion status consisting of the following details: (1) studies were required to include patients with radiological or pathological diagnosed bone metastases from breast cancer; (2) any dose of bone-targeted agent being used was considered to be eligible; (3) no specific criteria relating to duration of treatment with a bone-targeted agent prior to study entry was employed. The clinical outcomes of interest, skeletal related events (SREs), were defined to consist of multiple events which included pathologic fractures, radiotherapy/surgery to bone, spinal cord compression and hypercalcaemia of malignancy. Only validated measures of bone pain [e.g. The Brief Pain Inventory (BPI) and Functional Assessment of Cancer Therapy-Bone Pain (FACT-BP)] and quality of life (e.g. FACT-G, EORTC QLQ-BM22, EORTC QLQ-C15-PAL) were accepted. While the above noted outcomes were of primary interest, studies of relevant design, treatment and patients were still retained even if limited to other outcome measures in order to present a complete overview of the literature.

2.2. Literature search

An information specialist (KC) designed and executed an electronic literature search to seek relevant citations for this systematic review from Ovid Medline (1946-present), PubMed (for non-Medline records), the Cochrane Library (search run March 13, 2013), and from the three major annual oncology conferences held worldwide since 2010 (American Society of Clinical Oncology, the European Society for Medical Oncology, and the San Antonio Breast Cancer Symposium). The full literature search is provided as a supplement to this review (Appendices 1–3). As one of the applicants is also an expert in this field (MC), awareness of the area and contact with other experts was also used as an additional means to identify relevant ongoing work. These efforts did not identify any additional publications.

2.3. Study screening, selection, and risk of bias assessment

Two reviewers with expertise in oncology (MC, CA) reviewed the citations that were retrieved from the literature search independently. Stage 1 review consisted of screening of titles and abstracts only, while Stage 2 screening consisted of screening of full text articles where available to confirm study selection, or in the case of meeting abstracts, these were limited to their existing text. Following screening at each stage, the reviewers planned to meet to resolve any discrepancies and to consult a third party (BH) if needed. Results from the screening process are presented in a PRISMA flow diagram (Fig. 1) [15]. A list of included and excluded studies is provided in Appendix 4.

Risk of bias of all eligible randomized controlled trials was to be assessed using the Jadad scale [16]. However, it was found that only one included study was published in manuscript form, while the remaining studies were published in abstract form only. As a consequence, an assessment of only one eligible study [10] could be performed. Data collection from relevant studies was performed by the two reviewers using a pre-designed extraction form.

2.4. Data analysis

If deemed appropriate following exploration of study and patient characteristics to ensure sufficient clinical and methodological homogeneity across studies, we planned to pursue meta-analyses using random effects models to combine data for outcomes of interest across relevant studies, as described in the Cochrane Handbook [17]. Summary estimates were planned to be reported using appropriate point estimates and corresponding 95% confidence intervals, along with forest plots of all study estimates to provide visualization of variability in findings from study to study for each outcome. Statistical heterogeneity was also to be assessed using both the Cochrane Q statistic and the I^2 statistic. Following review of the included studies' characteristics, in particular with regard to patient populations, it was judged by the authors there were important clinical differences that precluded the data from meta-analysis. These differences are discussed in the summary of findings below. Given these differences, a narrative approach to summary of study-specific results was employed.

3. Results

3.1. Eligible studies

Our electronic literature search identified a total of 777 unique citations for review following removal of duplicates. Stage 1 screening identified a total of 7 citations which were considered potentially eligible for inclusion; 4 were meeting abstracts with no further information available which were thus included as is at Stage 2 screening, while 3 were associated with full manuscripts that were retrieved and screened. After Stage 2 screening, a total of 5 studies consisting of 1287 patients were included [10,11,13,18,19] while 2 were excluded because, while on topic, they were non-randomised, single-arm studies and thus did not fully meet pre-specified inclusion criteria [20,21]. Fig. 1 provides an overview of the process of study selection.