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Systematic review and meta-analysis on the proportion of patients with breast cancer who develop bone metastases

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ABSTRACT

A systematic literature review was conducted to quantify populations of patients with primary breast cancer in whom bone metastases were detected at study start or during follow-up. Searches were performed in PubMed and EMBASE using terms related to breast cancer and bone metastases. Articles had to have been published 01/01/99–31/12/13, and to report data on the proportion of patients with bone metastases among patients with breast cancer. In total, 156 articles were included in the meta-analysis. A median of 12% of patients with stage I–III breast cancer developed bone metastases during a median follow-up of 60 months. Of patients who developed metastatic disease during follow-up, 55% (median) had bone metastases. Of those with metastatic breast cancer at study start, 58% (median) had bone metastases. These data help to inform on the global burden of bone metastases by defining patient populations that are at risk of developing bone metastases.

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1. Background

Recent data report the age-standardised incidence of breast cancer in the European Union (27 countries) to be 108.8 per 100,000 women (Ferlay et al., 2013). In autopsy studies, bone metastases have been reported to occur in 65–75% of patients with metastatic breast cancer (Coleman, 2001). Data show that patients with breast cancer survive a median of 24–55 months after detection of bone metastases (Ahn et al., 2013; Coleman and Rubens, 1987; Domchek et al., 2000). Bone metastases in patients with breast cancer most commonly develop in the spine, ribs, pelvis and long bones (Chen et al., 2010), and the majority of patients who develop bone metastases at first relapse will experience bone complications such as pain, hypercalcaemia of malignancy and skeletal-related events (SREs) (Coleman, 2006). SREs include pathologic fracture, spinal cord compression and radiation or surgery to the bone (Coleman, 2006) and are associated with significant morbidity and poor survival: median survival for patients with bone metastases and a subsequent SRE is 7 months (Yong et al., 2011). SREs also greatly impact patient quality of life owing to an increase in pain, and a reduction in mobility and social function (Coleman, 2001; Costa et al., 2008; von Moos et al., 2016).

Patients with bone metastases secondary to breast cancer often receive local external-beam radiotherapy, which is highly effective for palliation of bone pain. Radiopharmaceuticals, such as strontium-89 and samarium-153, have also been demonstrated to provide effective pain relief in patients with osteoblastic or mixed osteoblastic/osteolytic bone metastases (Paes and Serafini, 2010; Silberstein, 2005; Yamada et al., 2012; Coleman et al., 2014a). The evaluation of newer α-emitting therapies such as radium-223 in patients with breast cancer and bone metastases is ongoing, with an initial phase 2 bone marker study (Coleman et al., 2014b) and preclinical research showing a positive treatment effect (Suominen et al., 2013). Advances in anticancer treatments, such as the highly specific aromatase inhibitors (letrozole, anastrozole and exemestane), have led to improved patient outcomes and reduced recurrence rates (Dowsett et al., 2010), however the impact of these agents on the risk of bone complications is controversial (Giusti et al., 2011).

The introduction of bisphosphonates (e.g. clodronate, pamidronate and zoledronic acid) has greatly lengthened the time to first SRE and thus reduced the overall number of SREs a patient will experience (Hortobagyi et al., 1998; Kohno et al., 2005; Kristensen et al., 1999; Lipton et al., 2000; Mathew and Brufsky, 2015; Paterson et al., 1993; Theriault et al., 1999; Body et al., 1998). Phase 2 and 3 studies have demonstrated that zoledronic acid is a highly effective bisphosphonate for the prevention of SREs in patients with bone metastases (Clemons et al., 2006; Rosen et al., 2004). Bone-targeted therapy with denosumab, which is directed against the receptor activator of nuclear factor κ ligand (RANKL), has demonstrated superiority over zoledronic acid, in a phase 3 trial, in delaying or preventing SREs in patients with breast cancer and bone metastases (Stopeck et al., 2010; Body, 2012). Moreover, preclinical evidence suggests that bone-targeted agents (BTAs) may prevent bone metastases by changing the bone microenvironment via direct and indirect inhibition of growth factor and cytokine signalling between the tumour and bone (Canon et al., 2008; Padalecki and Guise, 2002; Coleman et al., 2013a). Clinical trials and a meta-analysis have demonstrated that BTAs may reduce the risk of recurrence; however, the benefit appears to be limited to specific patient subgroups and further research is required to fully understand the role of adjuvant treatment with a BTAs in early stage breast cancer (Gnant et al., 2015a,b; Coleman et al., 2014c, 2015).

With an increasing interest in treatments that directly target the bone microenvironment (Coleman et al., 2013a), it is becoming more important to understand the size of the patient population that can be expected to develop bone metastases during the natural course of their disease. Limited data on metastatic bone disease in patients with breast cancer exists, with the majority coming from placebo-arms of clinical trials, single-centre cohort studies or retrospective database or autopsy analyses. We conducted a systematic literature review and meta-analysis to produce a quantitative summary of the proportion of patients with breast cancer and bone metastases either at study start or during follow-up.

2. Methods

A systematic literature review and meta-analysis of all published studies reporting on the proportion of patients with breast cancer and bone metastases was conducted.

2.1. Information sources and search terms

Searches were performed using Medline (PubMed) and EMBASE. Articles were limited to publication dates between 1 January 1999 and 31 December 2013. Filters were applied to restrict articles to English-language and human studies. In PubMed, the search terms used were: (“bone metastasis” OR “bone metastases” OR “metastatic bone”) AND (“cancer” OR “oncology” OR “breast cancer” OR “breast neoplasms”). Publication type was restricted by applying the “NOT review” filter. In EMBASE, the search terms employed were: (“bone metastasis”.mp. OR bone metastasis/OR “bone metastases”.mp. OR “metastatic bone”.mp.) AND (neoplasm/OR oncology/OR breast cancer/OR breast carcinoma/). To exclude review articles, the publication types “article” and “article in press” were selected. Following a review of search terms, an update to the initial searches was performed with additional search terms, including neoplasm (a Medical Subject Headings term in PubMed) and carcinoma. Publication dates and filters were applied as before.

2.2. Inclusion/exclusion criteria

Publications were included if they reported data from either a clinical trial (phase 1–4) or a prospective or retrospective observational study. All other publication types (comments, editorials, letters, correspondence, case reports, conference proceedings, reviews, etc.) were excluded. To be included, a full, peer-reviewed, English-language publication was required (i.e. publications with only an English-language abstract were discarded). For studies for which numerous publications existed discussing the same patient population, the most complete and/or up-to-date publication was used. Studies had to report data on the proportion of patients with bone metastases among patients with primary breast cancer.

Studies were excluded if they did not report the presence or development of bone metastases or if they published combined data on patients with different types of primary cancer. Studies were also excluded if they required patients to have evidence of bone metastases at study entry, presented data on only one location of bone metastases (e.g. spinal metastases only) or reported data only on the site of first progression or first metastases. Studies in which the patient population was not clearly described or in which there were data inconsistencies/inaccuracies or in which reported data were incomplete for our purposes, as determined by all authors, were also excluded.

2.3. Study selection and data extraction

Search results from the two databases were combined and duplicates removed. Titles and abstracts were screened to determine whether they met the pre-specified inclusion criteria. Full