Journal of Bone Oncology 11 (2018) 38–50

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Review Article

Incidence, risk factors and prognostic characteristics of bone metastases and skeletal-related events (SREs) in breast cancer patients: A systematic review of the real world data

Hongwei Zhang[b,1], Wei Zhu[b,1], Ewelina Biskup[c,d,1], Weige Yang[b], Ziang Yang[b], Hong Wang[b], Xiaochun Qiu[e], Chengjiao Zhang[f], Guangxia Hu[g], Guangfu Hu[a,*]

[a] Department of Breast Surgery, Shanghai Huangpu District Central Hospital, 200002, Shanghai, China
[b] Department of General Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China
[c] Shanghai University of Medicine and Health Sciences, Shanghai 201318, China
[d] Department of Internal Medicine, University Hospital of Basel, University of Basel, Petersgraben 4, 4051 Basel, Switzerland
[e] Medical School Library, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China
[f] Department of Psychological Measurement, Shanghai Mental Health Center, Shanghai, Jiao Tong University School of Medicine, Shanghai 200030, China
[g] Department of Pathology, Yankuang Group General Hospital, Zoucheng 273500, Shandong Province, China

ARTICLE INFO

Keywords:
Breast cancer
Bone metastases
Skeletal related events
Real-world data
Systematic review

ABSTRACT

Purpose: The aim was to systematically extrapolate the occurrence, risk factors, prognostic characteristics, management and outcome of bone metastases (BM) and skeletal related events (SREs) of breast cancer survivors in the real world clinical setting.

Methods: A systematic literature search of PubMed, Web of Science, EMBASE OvidSP and EBSCO Academic Search Complete was conducted. Published prospective and retrospective papers investigating BM and SREs in breast cancer patients in non-trial settings were identified and systematically reviewed.

Results: Twenty-four studies met the inclusion criteria. Incidences of BM based on new diagnosis, length of BM-free interval (BMFI) and number and sites of BM were detected by 17 of 24 studies. Seven studies included in the review were subjected to analyses of risk factors for BM. Developments of SREs regarding the occurrence ratio of total and specific SREs, SERs-free interval (SREFI) and the first-line therapy for SREs were observed in 16 of 24 studies. Out of 5 studies, we extracted uni- and multivariate analysis of risk factor for SREs and out of 16 studies - predictors for survival in breast cancer patients with BM.

Conclusions: BM and SREs are common problems in non-trial breast cancer populations. Patient demographics, clinical stage, tumor pathological type, molecular receptors status are significantly risk factors for incidence of BM, SREs and the survival. The unique characteristics of BM and SREs in breast cancer patients should be taken into account in future randomized controlled trials, as to optimize individual treatment options and assure a maximally long good quality of life.

1. Background

Breast cancer is the most common cancer in females worldwide [1,2]. Significant progress in prophylaxis, diagnosis and management of breast cancer has been made, especially in the last decade [3,4]. However, female deaths by breast cancer did not decrease since advances in treatment merely compensated for the increasing incidence originating from demographical development and lifestyle changes [5,6]. Distant metastases are still the leading cause of death in breast cancer patients [7,8].

Bone is the most frequent site of breast cancer metastasis [9,10]. At the time of diagnosis of breast cancer approximately 5–6% of women present themselves with bone metastases (BM). In advanced stages of breast cancer, about 65–75% of patients eventually develop BM [11,12]. BM is associated with accelerated bone resorption leading to increased morbidity due to a range of skeletal-related events (SREs) including bone pain (BP), pathological fracture (PF), spinal cord compression (SCC), tumor-induced hypercalcemia (TIH) and surgery or radiation therapy (RT) to bone [13]. Not surprisingly, SREs often worsen quality of life, performance status, and independent

* Correspnding author.
E-mail address: guangfuhu12@fuadn.deu.cn (G. Hu).
[1] Hongwei Zhang, Wei Zhu and Ewelina Biskup have contributed equally to this work and co-first authors.

https://doi.org/10.1016/j.jbo.2018.01.004
Received 9 December 2017; Received in revised form 24 January 2018; Accepted 27 January 2018
Available online 03 February 2018

functioning. Studies have demonstrated that at least one SRE occurs in nearly 50% of patients with bone metastases of breast cancer [14,15]. Given the high prevalence of breast cancer, the population wide burden of BM is considerable. Thus, it is of immense important to analyze SREs and BM in the context of diagnosis, therapy and follow up.

Management options of breast cancer are based on surgical interventions, RT, neo- and adjuvant chemotherapy (ChT), hormonal therapy (HT) or molecular-targeted therapy (MT). The optimal, personalized management however, varies between patients according to cancer entity and physical status of the patient. In consequence comparability of patients with BM in clinical trials is limited. Furthermore few single-center, multi-center, and population-based studies specifically reporting BM and SREs exist. So far the systematic review or meta-analysis of these data is lacking. Therefore, we conducted review, focusing on incidence, risk factors, prognostic characteristics, management and outcome of BM and SREs in breast cancer patients. Our data provide the first coherent dataset that can be used for adjustments in care of breast cancer patients with BM and SREs in order to assure the best possible outcome, as well as to avoid an over-or under-treatment with BM and SREs.

2. Methods

Several breast surgeons, a medical oncologist and a medical statistician formed the panel to develop the search, selection, and review strategies, based on guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16,17].

2.1. Sources and search strategy

Literature research was performed independently by two trained reviewers (GF.H. and E.B.) using Pubmed, Web of Science, EMBASE OvidSP and EBSCO Academic Search Complete for articles published between 2000 and 2017 on English-language studies related to breast cancer, BM and SREs. The search was conducted using Medical Subject Headings (MeSH) or keywords, and when appropriate, search terms. Search terms were Boolean search criteria and included “Breast Neoplasms”, “Breast Cancer”, “Breast Carcinoma” OR “Breast Tumor*” and “Bone metastases”, “Bone metastasis”, “Metastasis of Bone”, “Metastases of Bone”, “Skeletal metastases”, “Skeletal metastasis”, “Skeletal complication*” OR “Skeletal-related event*”. Further manuscripts were identified from reference lists of the primary papers. The last search was performed on June 11th, 2017. Detailed search methods are provided in the supplemental file (Appendix A–D).

2.2. Eligibility criteria

The records obtained from the literature search, containing titles and abstracts of the reviews, were exported into Refworks. First, duplicates were identified and removed from the pool of bibliographic records. Then, two trained investigators (GF.H. and E.B.) independently screened all retrieved abstracts and titles to determine articles that were ‘‘potentially” and deemed “relevant” references. Afterwards, two further reviewers (W.Y., H.W.) independently reviewed the full articles, using the following inclusion criteria: (1) single-center, multi-center or population-based clinical studies, focusing on breast cancer patients with BM; (2) studies that provided clinical information and specific data on the outcome of patients with BM from breast cancer. Studies were excluded if (1) they were single case reports, regular reviews or systematic review articles; (2) clinical trials focusing on breast cancer treatment; (3) studies on metastatic breast cancer focusing on visceral metastases; (4) investigating other cancers besides metastatic breast cancer. Disagreements were resolved by consulting with three additional reviewers (W.Z., Z.Y., H.Z.). When studies of overlapping groups of patients were identified, only the most recent studies were retained, with the notable exception of earlier studies presenting analyses that were not repeated in the most recent study.

2.3. Quality assessment

Two reviewers (C.Z. and GX.H.) independently assessed the quality of all included studies according to the Newcastle-Ottawa Scale (NOS) [18,19]. The NOS has been developed to assess the quality of case–-control and cohort studies, containing three parameters of quality that included: (1) selection; (2) comparability; and (3) exposure/ outcome assessment. Studies that achieved five or more points were considered to be of high quality. Any discrepancies between reviewers were addressed by a joint reevaluation of the original article.

2.4. Data abstraction

Two investigators (GF.H. and C.Z.) independently abstracted the data from the included articles. First author's name, publication year of the article, patients’ data (demographics, tumor characteristics, BM) were extracted from each study. Any univariate and multivariate analysis for risk factors for BM and SREs or prognostic factors affecting survival in patients with breast cancer BM were tabulated. Whenever possible, diagnostics of BM, development of SREs, treatment information and prognostic outcomes were extracted. If these data were not mentioned explicitly in the manuscripts (e.g. number of SREs), they were extrapolated from graphs, tabulated proportions of events or from subgroup analyses. Any disagreements were discussed to reach a consensus agreement.

3. Results

3.1. Literature search

The literature search yielded 2469 bibliographic records. Of this initial pool of records, 2280 were excluded after the first screen of the titles and abstracts. Following the full-text review, 156 studies were rejected for being out of scope. Of the remaining 33 records, nine were removed applying the exclusion criteria. The final set of bibliographic records reviewed was composed of 24 studies [20–43] (Fig. 1).

3.2. Assessment of methodologic quality

The results of the quality assessment according to the NOS are shown in supplemental file (Appendix E). In total, 24 studies were included and all of which were assessed as high quality: One study [24] was rated with a NOS score of six, eight studies [23,26,28,33,36,37,41,42] with a NOS score of seven, six studies [21,22,32,34,39,40] with a NOS score of eight, seven studies [20,25,27,31,35,38,43] with a NOS score of nine, and two studies [29,30] with a NOS score of ten.

3.3. Characteristics of the studies

Characteristics of the studies regarding study type and sample size, BM occurrence rates, patient demographics, tumor histopathological findings and clinical stage, estrogen receptor (ER) expression status, progesterone receptor (PR) expression status, epidermal growth factor receptor 2 (HER2) status, follow-up period are described in Table 1. The 24 studies selected according to the inclusion criteria were published between 2000 and 2016. The median follow-up period ranged from 1.12 [21] to 12.50 years [20]. The BM occurrence rates ranged from 4.1% [40] to 30% [30]. The number of patients enrolled ranged from 48 [37] to 7189 patients [32], of whom only one was male [23]. The median patients age at the time of diagnosis of breast cancer ranged from 46 [38] to 75 [32]. Premenopausal status reported in eight studies ranged from 13% [39] to 80% [30]. In total, hormone receptor (ER and/or PR) positive breast cancer was most common, followed by HER2