The Breast 37 (2018) 28–35

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

Therapeutic approaches for protecting bone health in patients with breast cancer

Diana Lüftner [a], Daniela Niepel [b], Guenther G. Steger [c, d, *]

[a] University Hospital Berlin, Charité Campus Benjamin Franklin, Berlin, Germany
[b] Amgen (Europe) GmbH, Vienna, Austria
[c] Department of Medicine, Clinical Division of Oncology, Comprehensive Cancer Centre, Medical University of Vienna, Vienna, Austria
[d] Gaston H. Glock Research Center, Vienna, Austria

ARTICLE INFO

Article history:
Received 23 August 2017
Received in revised form
12 October 2017
Accepted 13 October 2017

Keywords:
Bone metastasis
Bisphosphonate
Breast cancer
Cancer treatment-induced bone loss
Denosumab
Zoledronic acid

ABSTRACT

Improvements in the survival of patients with breast cancer, together with a better understanding of the pathology of the disease, have led to the emergence of bone health as a key aspect of patient management. Patients with breast cancer are typically at risk of skeletal complications throughout their disease course. The receptor activator of nuclear factor κ B ligand (RANKL) inhibitor denosumab and bisphosphonates (e.g. zoledronic acid) are approved in Europe for the prevention of skeletal-related events (pathologic fracture, radiation or surgery to bone, and spinal cord compression) in adults with bone metastases secondary to solid tumours. These agents are also approved at lower doses for the treatment of patients with postmenopausal osteoporosis, a population largely overlapping with those in the early stages of breast cancer, and those with cancer treatment-induced bone loss, which is caused primarily by aromatase inhibitors. In this review, we consider the evidence supporting the use of therapeutic agents to protect bone health throughout the course of breast cancer. Timing of treatment initiation, dose and treatment duration may prove to be barriers to the optimization of the practical use of these agents in the management of patients with breast cancer. Furthermore, with longer survival times, patients may expect to receive long-term treatment with denosumab or bisphosphonates, therefore consideration must be given to safety. Thus, we aim to summarize the recommendations for the use of these agents in management of patients with breast cancer in Europe. We also discuss the recent evidence for their potential antineoplastic effects.

Contents

* Corresponding author. Department of Medicine, Clinical Division of Oncology, Comprehensive Cancer Centre, Medical University of Vienna, Spitalgasse 23, BT86/E01, 1090, Vienna, Austria.
E-mail address: guenther.steger@meduniwien.ac.at (G.G. Steger).

https://doi.org/10.1016/j.breast.2017.10.007
0960-9776/

1. Introduction

Survival for patients with breast cancer in Europe has improved substantially over the past three decades. Between 1989 and 1999, 5-year age-adjusted relative survival increased from 74% to 83% [1], and 5-year survival reached 82% for patients in whom breast cancer was diagnosed between 2000 and 2007 [2]. Recent age-standardized data from the United Kingdom predict 5-year survival of 86.6% for patients diagnosed between 2010 and 2011 [3]. Current levels of expectation for survival are due, in part, to the establishment of European breast cancer screening programmes and improved treatment options [4]. With increased survival comes a greater requirement for the long-term holistic care of patients than ever before [5].

Clinical experience of the long-term management of breast cancer has led to an appreciation of the importance of bone health throughout the disease course. The mean age at breast cancer diagnosis is 62 years [6], and because most patients are perimenopausal or postmenopausal women, they may already have experienced some osteopenic or osteoporotic bone loss. With the onset of menopause, declining oestrogen levels lead to a gradual decrease in bone mineral density (BMD) over time, with the potential for the development of postmenopausal osteoporosis [7]. A decrease in BMD may be exacerbated by the bone-destabilizing effects of certain cancer treatments used in early breast cancer, such as aromatase inhibitors, which can induce a menopause-equivalent state by reducing oestrogen levels, and some chemotherapies. This phenomenon is known as cancer treatment-induced bone loss (CTIBL) [8]. The rate of bone loss in women with breast cancer receiving aromatase inhibitors is at least twice that observed in healthy postmenopausal women [9]. In addition, more than 60% of women initiating chemotherapy are expected to experience ovarian failure within 1 year [10], which is associated with further significant and rapid declines in BMD [11]. Reductions in BMD cause skeletal weakening and increase the risk of pathologic fracture; indeed, the 3-year risk of vertebral fracture is almost fivefold greater in women with newly diagnosed breast cancer than in women in the general population [12]. It is important to note that, even in individuals with normal BMD, the risk of fracture in patients with breast cancer is high. For example, in the placebo arm of the Austrian Breast and Colorectal Cancer Study Group-18 (ABCSG-18) trial in postmenopausal women with early-stage breast cancer, the incidence of pathologic fracture was 10% in individuals with normal BMD and 11% in those with low BMD [13].

Osteoporosis can be treated with low doses of the receptor activator of nuclear factor κ B ligand (RANKL) inhibitor denosumab (60 mg subcutaneously [SC] every 6 months) [14,15] or with bisphosphonates, the most commonly used being zoledronic acid (5 mg intravenously [IV] once per year) [16]. Denosumab offers concurrent benefit to women at risk of CTIBL in the early, hormone-receptor-positive (HR+) stages of breast cancer because these patients are considered at risk for osteoporosis. Evidence suggests that adjuvant use of low-dose denosumab in patients with HR+ breast cancer [13] or adjuvant zoledronic acid in early breast cancer [13,17,18] may positively impact on outcomes in certain populations, although this is not currently reflected in product indications. Disturbances in bone metabolism can be caused by the underlying pathology of the cancer or by bone metastases, and may result in some patients developing hypercalcaemia of malignancy, which is associated with a poor prognosis [19]. With some regional variation, denosumab and zoledronic acid are also approved for the treatment of hypercalcaemia of malignancy [20–22].

As breast cancer progresses, the risk of developing bone metastases increases. For patients with aggressive breast cancer, distant metastases can occur during the 3 years after diagnosis of the primary cancer; however, many patients develop distant metastases as much as 10 years after their initial diagnosis [23]. In Western women with breast cancer, metastases at distant sites are a more common cause of death than the primary tumour itself [23]. Bone is one of the most common sites of metastases from breast cancer, with an incidence of approximately 70% [23,24]. Bone metastases cause complications, commonly referred to as skeletal-related events (SREs; pathologic fracture, spinal cord compression, and radiation or surgery to bone) and are associated with substantial pain and reduced survival [25].

An improved understanding of the importance of bone health in patients with breast cancer has brought about changes in the clinical management of these individuals. For those with breast cancer and bone metastases, denosumab (120 mg SC every 4 weeks) [26] and zoledronic acid (4 mg IV every 3–4 weeks) [21] can prevent SREs [27,28] and offer improvements in quality of life [29,30]. Better detection of bone metastases as a result of improved diagnostic techniques and monitoring [31], and heightened patient awareness through channels such as patient advocacy websites [32], are facilitating earlier intervention with these agents. In this review, we aim to consolidate the latest understanding on the use of denosumab and bisphosphonates for protecting skeletal health in women with breast cancer at all stages of their disease.

2. Early breast cancer

Skeletal weakening due to CTIBL and postmenopausal osteoporosis, as well as the potential for subsequent increases in pathologic fracture risk, are major concerns for patients with early breast cancer. Aromatase inhibitors are routinely used in the adjuvant treatment of HR+ early breast cancer in postmenopausal women; however, through the induction of oestrogen deficiency, the agents can cause a negative bone balance, with increased markers of bone resorption, as well as decreased BMD and increased fracture risk [8]. This has been demonstrated in a prospective substudy of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, which had previously demonstrated clinical superiority of the aromatase inhibitor anastrozole over tamoxifen in postmenopausal women with breast cancer [33]. In the substudy, long-term use of anastrozole resulted in median BMD losses from baseline of 6.1% at the lumbar spine and 7.2% from the total hip after 5 years [34]. Increases of 2.8% and 0.7% at the lumbar spine and total hip, respectively, were observed with tamoxifen [34]. Accordingly, the incidence of fractures was significantly lower in those who received tamoxifen than in those prescribed anastrozole (4.4% vs. 7.1%; $p < 0.001$). Although aromatase inhibitors are a common cause of CTIBL, reductions in BMD may also result from treatment with certain chemotherapies, by means of upregulated bone resorption. Drugs likely to produce this effect include taxanes, doxorubicin, 5-fluorouracil, cyclophosphamide, methotrexate and cisplatin [8].