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Research Paper

Bone-targeted agent treatment patterns and the impact of bone metastases on patients with advanced breast cancer in real-world practice in six European countries

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ABSTRACT

Background: Bone metastases (BMs) are common in patients with breast cancer and can lead to skeletal-related events (SREs), which are associated with increased pain and reduced quality of life (QoL). Bone-targeted agents (BTAs), like zoledronic acid and denosumab, reduce the incidence of SREs and delay progression of bone pain.
Materials and methods: We evaluated the management of BMs and pain in six European countries (Belgium, France, Germany, Italy, Spain, and UK) using the Adelphi Breast Cancer Disease Specific Programme, which included a physician survey and patient-reported outcomes (PROs) to assess the impact of BMs on pain and QoL.
Results: 301 physicians completed patient record forms for 2984 patients with advanced breast cancer; 1408 with BMs and 1136 with metastases at sites other than bone (non-BMs). Most patients with BMs (88%) received a BTA, with 81% receiving treatment during 3 months following BM diagnosis. For those who did not receive a BTA, the main reasons given were: very recent BM diagnosis, perceived low risk of bone complications, and short life expectancy. Most patients with BMs (68%) were experiencing bone pain and, of these, 97% were taking analgesics (including 28% receiving strong opioids). Despite this, moderate to severe pain was reported in 20% of patients who were experiencing pain. PROs were assessed in 766 patients with advanced breast cancer (392 with BMs, 374 with non-BMs). Overall, patients with BMs reported worse pain and QoL outcomes than those with non-BMs, those not receiving a BTA reported worse pain.
Conclusion: Despite the large proportion of patients receiving BTAs in this study, some patients with BMs are still not receiving early treatment to prevent SREs or to manage pain. Improving physicians' understanding of the role of BTAs and the importance of early treatment following BM diagnosis has the potential to improve patient care.

1. Introduction

Bone is the most common site affected by metastatic cancer: a recent meta-analysis reported that bone metastases (BMs) occur in 58% of patients with advanced breast cancer [1]. BMs often cause debilitating bone pain and lead to bone complications, known as skeletal-related events (SREs; commonly defined as radiation or surgery to bone, pathologic fracture, spinal cord compression, or hypercalcemia of malignancy) [2]. SREs cause pain, impair physical activity, negatively affect quality of life (QoL), and are associated with increased mortality [3–5]. Clinical trial data show that, if patients do not receive treatment to prevent SREs, 64% of women with breast cancer and BMs develop an SRE [6]. In the real-world setting, the SRE incidence is probably lower than that from clinical trials. This may be because symptomatic SREs

Abbreviations: BMs, bone metastases; BPI, Brief Pain Inventory; BTA, bone-targeted agent; CI, confidence interval; DSP, Disease Specific Programme; EQ-5D, 5-dimension (3-level) EuroQol questionnaire; ER, estrogen receptor; FACT-B, Functional Assessment of Cancer Therapy – Breast questionnaire; HER2, human epidermal growth factor receptor 2; ONJ, osteonecrosis of the jaw; PRO, patient-reported outcome; PRF, Patient Record Form; PSCF, Patient Self-Completion Form; QoL, quality of life; SRE, Skeletal-related event; ZA, zoledronic acid

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(SSEs) are more likely to be collected than SREs and reflects real-world practice that some patients may receive treatment to prevent SREs. The high prevalence of SREs in patients with advanced breast cancer reflects both the high incidence of BMs [7] and the relatively long survival times in these patients [8]; metastatic breast cancer at diagnosis is associated with 3-year and 5-year survival rates of approximately 35% [9] and 26%, respectively [10]. Patients with BMs generally survive for longer than patients with other metastatic sites (such as liver, brain, or lung) [11]. Furthermore, individuals with advanced breast cancer may experience several SREs during the course of their disease [12], and having one SRE increases a patient's risk of experiencing subsequent SREs [13]. These bone complications therefore place a considerable burden on both patients and healthcare resources [14–16].

Bone-targeted agents (BTAs), such as the bisphosphonate zoledronic acid (ZA) and denosumab, reduce the incidence of SREs [17,18] and delay the progression of bone pain [19]. ZA is administered as a 4 mg intravenous infusion every 3–4 weeks [17]; denosumab, a fully human immunoglobulin G2 monoclonal antibody against the receptor activator of nuclear factor kappa B ligand, is administered as a 120 mg subcutaneous injection every 4 weeks [18]. These therapies have both been shown to delay SREs [17,18] and reduce pain levels in patients with moderate to severe pain [19]; denosumab has been shown to be more effective than ZA at delaying and preventing SREs, preventing the worsening of pain associated with BMs, and delaying the need for strong opioids [19]. Both agents are recommended for patients with BMs whether they are symptomatic or not [20]. Pain is often underreported and poorly managed in patients with cancer [21]. In a phase 3 trial evaluating denosumab versus ZA in patients with BMs secondary to breast cancer, 43% of patients had moderate to severe bone pain at the start of BTA treatment; however, fewer than 20% of these patients were receiving strong opioids [22]. Little is known about the utilization pattern of BTAs and the impact of BMs in real-world practice.

2. Aims

This study aimed to describe the treatment pattern of BTAs in patients with breast cancer and BMs, including the reasons guiding treatment decisions, in a real-world setting in Europe. Furthermore, by using validated instruments to collect patient-reported outcomes (PROs), we aimed to understand the impact of BMs on patients' experiences of pain and QoL.

3. Methods

3.1. Physicians and patients

Data were collected using the Adelphi Breast Cancer Disease Specific Programme (DSP), an independent multi-country, cross-sectional survey of physicians. The full DSP methodology has been described previously [23]. The study was conducted between February and April 2015 in six European countries comprising Belgium, France, Germany, Italy, Spain, and the UK. Physicians were selected from publicly available lists of healthcare professionals, and were approached to take part in the study by field-based interviewers. The study aimed to gain participation from 300 physicians (60 in each of France, Germany, Italy, and Spain, 50 in the UK, and 10 in Belgium). To be eligible for inclusion in the study, physicians had to have: medically qualified as an oncologist between 1978 and 2011; been seeing a minimum of five patients with breast cancer per week; and been personally responsible for prescribing decisions for patients with advanced breast cancer.

Participating physicians reported data for the next eight consecutive adult (aged ≥18 years) female patients they saw in their clinic who had been diagnosed with advanced breast cancer (stage IIIB–IV) and who were not currently enrolled in a clinical trial. Physicians also collected data from a further two patients with the additional criterion of a BM diagnosis. Physicians captured data using a detailed Patient Record Form (PRF) for each of the 10 patients; data were included regardless of how many patients physicians filled out a PRF. All patients for whom a physician completed a PRF were invited to complete a voluntary Patient Self-Completion Form (PSCF). Informed consent was obtained from patients before they completed this form.

3.2. Study variables

Data on patient baseline characteristics were extracted from all the PRFs. For patients with a BM diagnosis the following data were also collected from the PRFs: presence of bone pain (at initial diagnosis of BMs and at time of data collection – pain was classified as mild, moderate, or severe according to the Brief Pain Inventory [BPI]) [24]; analgesic use (measured using the modified Analgesic Quantification Algorithm [25], which scores analgesic use from 0 for no analgesic to 7 for strong opioid [> 600 mg/day oral morphine equivalent]); time from initial breast cancer diagnosis to BM diagnosis; time from BM diagnosis to the date of data collection; whether a BTA was prescribed; time from BM diagnosis to BTA treatment initiation; which BTA was prescribed; the dose of BTA; discontinuation of a BTA; and switching from one BTA to another.

Physicians were asked to rank up to three reasons from a predefined list for: treating or not treating patients with a BTA; choosing one BTA over another; changing BTA dose; switching from one BTA agent to another; and discontinuing BTA therapy. To understand whether BTA treatment was initiated immediately after BM diagnosis or not, a cutoff period of 3 months from diagnosis of BMs to treatment initiation was used. Physicians were asked to rank their reasons for initiating BTA treatment early (≤3 months of BM diagnosis) or for delaying BTA treatment (> 3 months after BM diagnosis).

The PSCFs incorporated three instruments to facilitate the collection of PRO data on pain and QoL from patients with BMs and from those with metastases located at sites other than the bone (non-BMs), which included the BPI [24], the 5-dimension 3-level EuroQol questionnaire (EQ-5D), the EuroQol visual analog scale (EQ-VAS) [26], the Functional Assessment of Cancer Therapy – Breast questionnaire (FACT-B), and the Functional Assessment of Cancer Therapy – General questionnaires [27].

3.3. Statistical analyses

Patient characteristics and outcome variables were analyzed using descriptive statistics. Frequencies (%) were calculated for categorical or ordinal variables, and means and medians (interquartile ranges) for continuous variables. PROs for patients with BMs and those with non-BMs were compared using the univariate Mann–Whitney test and multivariable linear regression analysis (adjusting for confounding factors: age, smoking status, time since diagnosis of breast cancer, positive estrogen receptor [ER] status, positive human epidermal growth factor receptor 2 [HER2] status, and number of additional comorbidities).

4. Results

4.1. Physician characteristics

In total, 301 oncologists (11 in Belgium, 55 in France, 62 in Germany, 61 in Italy, 61 in Spain, and 51 in the UK) provided data via PRFs. Of these, 84 physicians stated that they worked in an office setting; 73% worked in public practice and 26% in private practice.

4.2. Patient characteristics

Data were collected for 2984 patients with advanced breast cancer. Of these, 2544 had metastatic (stage IV) cancer, including 1408 with