Research Paper

Age-related differences in persistence with bisphosphonates in women with metastatic breast cancer

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ABSTRACT

Aims: To investigate age-related persistence with bisphosphonates (BIS) in women with breast cancer (BC) and bone metastases.
Methods: We included a dataset of 1541 patients diagnosed with BC and bone metastases and initially treated with BIS between 1994 and 2013. The primary outcome measure was the age-related rate of BIS discontinuation within 12 months after treatment initiation. Therapy discontinuation was defined as a period of at least 90 days without treatment. A multivariate Cox regression model was created to determine the influence of age on the risk of discontinuation. Health insurance coverage (private/statutory), type of care (gynecological/general), region (West/East Germany), depression, chemotherapy, hormone therapy, pain medication, antidepressants, and the number of co-medications were included as covariates.
Results: The mean ages in the group of women < 70 and that of women ≥ 70 years of age were 55.7 (SD: 9.8) and 76.7 (SD: 5.1) years respectively. Within 12 months after treatment initiation, 44.3% of women < 70 and 34.8% of women ≥ 70 had terminated treatment (p-value < 0.001). Patients aged ≥ 70 were at a lower risk of treatment discontinuation than patients < 70 (HR=0.78, 95% CI: 0.67–0.91). Furthermore, treatment in gynecological practices, chemotherapy, hormone therapy, pain medication, and number of co-medications decreased the risk of discontinuation. By contrast, residing in West Germany and private health insurance coverage increased discontinuation risk.
Conclusions: Women with metastatic BC aged ≥ 70 are at a lower risk of BIS treatment discontinuation than younger women.

1. Introduction

Breast cancer (BC) is the most common cancer in women, with approximately 1.7 million new diagnoses in 2012. This figure represents about 25% of all new cancer cases in women and 12% of those in the general population [1]. Today, the median age at diagnosis is around 60 years and, since 20% of the global population will be aged > 65 years by 2030, the number of women diagnosed with BC in this age group is likely to increase in the future.

In women with BC, bone is the most common site of metastases [2–5]. Since bone lesions cause significant damage to the bone microstructure, patients with metastatic BC are at a high risk of skeletal-related events (SREs), such as bone pain, hypercalcemia, bone fracture, or spinal cord compression, which could potentially affect quality of life and life expectancy [6,7]. There are various bone metastasis treatments, depending on the number and the site of the lesions (i.e. radiotherapy, chemotherapy, or orthopedic intervention). Complementing these treatments is the role of bone-targeted agents such as bisphosphonates (BIS) [8,9]. Although no consensus has yet been reached on the optimal duration of BIS therapy, BIS use is generally recommended for a period of several years.

One significant problem associated with chronic conditions is the lack of treatment persistence and compliance. It has been demonstrated that around 50% of patients suffering from such conditions discontinue their therapy early [10]. In the case of BC, older women are known to be at a higher risk of treatment discontinuation than younger women [11]. This has also been demonstrated in several studies concerning the adjuvant treatment of women with BC. Consequently, lower persistence in older women with BC and bone metastases treated with BIS would lead to a reduced clinical benefit.

Recently, Hadji and colleagues demonstrated that persistence with intravenous and oral BIS is unexpectedly low and ought to be

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increased [12]. The aim of our study was to compare persistence with intravenous and oral breast cancer-related BIS treatment in younger (< 70) and older (≥ 70) women with BC treated in gynecological practices in Germany.

2. Methods

2.1. Database

The Disease Analyzer database (IMS HEALTH) compiles drug prescriptions, diagnoses, basic medical and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners [13]. Diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical (ATC) Classification System) and the quality of reported data have been monitored by IMS based on a number of criteria (e.g., completeness of documentation, linkage between diagnoses and prescriptions).

In Germany, the sampling methods used for the selection of physicians' practices were appropriate to obtain a representative database of general and gynecological practices [13]. Prescription statistics for several drugs were very similar to data available from pharmaceutical prescription reports [13]. The age groups for given diagnoses in Disease Analyzer also complied well with those in corresponding disease registries [13]. Finally, the Disease Analyzer database has already been used to perform studies on cancer, and more particularly BC, in Germany [1,14–16].

2.2. Study population

Overall, the database included 2067 general practices and 397 gynecological practices reporting to IMS HEALTH on a continuous basis during the study period. First-time cancer-related BIS prescriptions (ATC: M03B4) from January 1994 until December 2013 in subjects diagnosed with bone metastases (ICD 10: C795) following breast cancer diagnosis (ICD 10: C50) were defined as the index dates; the latest follow-up date was identified as April 2014.

Patients with a follow-up time of less than 365 days prior to the index date were excluded. This exclusion was necessary to ensure correct identification of treatment initiation. Further inclusion criteria comprised the following: age of over 18 years at the index date and no diagnosis of other tumors in the time between first BC diagnosis and first bone metastasis diagnosis.

A total of 1541 patients were available for persistence analysis. These patients were treated in 185 gynecological and 515 general practices.

Individuals were classified into two different groups: one including women under 70 years of age and one including women 70 years of age or over.

2.3. Study outcome

The main outcome measure was BIS treatment discontinuation rate within one year after the index date. Treatment discontinuation of a specific BIS therapy was defined as a period of 90 days devoid of this or an alternative BIS therapy within that time frame. Persistence is defined as the time from the beginning of therapy to therapy discontinuation.

A longitudinal dataset of medication supply was established for each individual patient and non-persistence with one of the study drugs (i.e. zoledronate, ibandronate, clodronate and pamidronate) was calculated. As part of this process, the number of days of drug supply was calculated on the basis of the quantity and dosage information associated with each prescription record. All patients were monitored for a duration of at least three months to one year from their index date in order to identify treatment discontinuation.

In addition, the share of patients switching treatment was calculated as patients commencing an alternative BIS therapy after the first day of discontinuation of the initial treatment. Patients restarting the initial treatment or starting another BIS therapy after 90 days without treatment were still classified as non-persistent, along with patients who discontinued their initial therapy and received no further BIS treatment. Patients restarting the initial therapy or starting another BIS therapy within 90 days were counted as persistent. Women who died during the study time frame were excluded from the analyses.

2.4. Covariates

Demographic data included age, health insurance coverage (private or statutory), gynecologist care, and practice region (East versus West Germany). Co-diagnoses of depression were determined based on primary care diagnoses (ICD-10 codes: F32, F33). Furthermore, the pre- or co-treatment was defined based on Anatomical Therapeutic Chemical Classification (ATC) for chemotherapy (L01, L02), endocrine treatment (tamoxifen or aromatase inhibitors), pain medication (ATC: N02A, N02B, M01A), and antidepressants (ATC: N06A). Finally, the number of co-medications was defined as the maximum number of different drugs a patient was prescribed to take in a single day.

2.5. Statistical analysis

Kaplan-Meier analyses were performed to examine treatment persistence in the two different age groups. A Cox proportional hazards regression model was used to estimate the relationship between non-persistence and age as well as the other demographical/clinical variables described previously. A p-value of < 0.05 was considered statistically significant. Analyses were carried out using SAS version 9.3.

3. Results

3.1. Patient characteristics

Patient characteristics are displayed in Table 1. A total of 1541 women with BC and bone metastases were included in this study, of which 1133 were < 70 (mean age=55.7, SD=9.8) and 408 ≥ 70 (mean age=76.7 and SD=5.1). The proportion of patients with private health insurance coverage, residing in West Germany and

Table 1
Baseline characteristics of women with breast cancer and bone metastasis receiving bisphosphonate treatment: IMS HEALTH Disease Analyzer, Germany.

Variables	< 70 years	> =70 years	p-Value
N	1133	408	
Age (years)	55.7 (9.8)	76.7 (5.1)	< 0.001
Gynecologist treatment (%)	50.1	40.4	< 0.001
Private health insurance coverage (%)	14.1	9.0	0.004
Region (West Germany) (%)	86.4	81.8	0.017
Intravenous bisphosphonates (%)	73.2	74.5	0.591
Co-diagnosis[a] *(%):*			
Depression	28.3	30.0	0.499
Co-treatment[b] *(%):*			
Chemotherapy	34.5	19.9	< 0.001
Hormone therapy	70.4	73.7	0.164
Antidepressants	23.4	22.4	0.669
Pain medication	58.0	62.0	0.128
Number of different drugs taken per day	2.9 (2.0)	3.2 (2.2)	0.019

Data are means (SD) or proportions (%).

[a] Diagnosis prior to index date or during bisphosphonate treatment.
[b] Prescriptions prior to index date or during bisphosphonate treatment.