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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.© 2016 The Authors. Published by Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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 (\geq 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 \geq 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	\geq 70 years	p -Value
<i>N</i>	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
<i>Co-diagnosis</i> ^a (%):			
Depression	28.3	30.0	0.499
<i>Co-treatment</i> ^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.

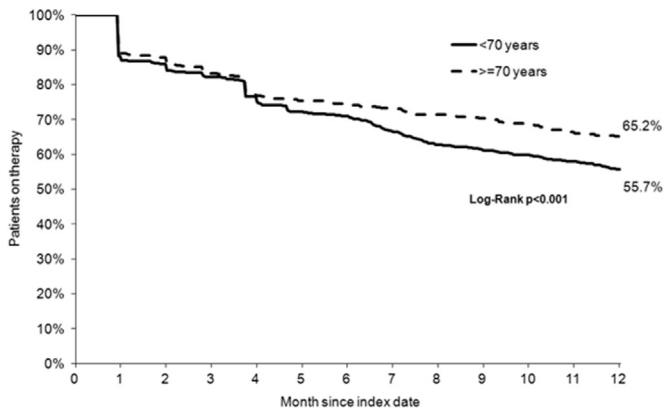


Fig. 1. Kaplan–Meier curves for persistence of women with breast cancer and bone metastases.

monitored in a gynecological practice was higher in the group of women aged < 70 than in the group of patients aged ≥ 70 (14.1% versus 9.0%, 86.4% versus 81.8% and 50.1% versus 40.4%; all p -values lower than 0.017). By contrast, the proportion of women receiving intravenous BIS as initial treatment and exhibiting dementia did not differ significantly between the two age groups (73.2% versus 74.5%, p -value=0.591; and 28.3% versus 30.0%, p -value=0.499). Finally, the use of chemotherapy was more common in the younger age group than in the older one (34.5% versus 19.9%, p -value < 0.001), whereas the use of endocrine treatment, antidepressants, and pain medications did not differ between the two groups. The number of drugs being taken was significantly higher in women aged ≥ 70 than in women < 70 (3.2 versus 2.9, p -value=0.019).

3.2. BIS treatment persistence

Fig. 1 displays Kaplan–Meier curves for the time to discontinuation of BIS treatment in women with BC and bone metastases as a function of age (< 70 versus ≥ 70). Within 12 months after treatment initiation, 44.3% of women < 70 and 34.8% of women aged ≥ 70 had discontinued treatment (Log-Rank p -value < 0.001). The results of the Cox regression model are shown in **Table 2**. Patients aged ≥ 70 were at a lower risk of BIS treatment discontinuation than patients < 70 (HR=0.78, 95% CI: 0.67–0.91 and p -value=0.001). While residing in West Germany and having private health insurance coverage increased the chances of disruption (HR=2.01, 95% CI: 1.60–2.52, p -value < 0.0001 , and HR=1.32, 95% CI: 1.07–1.62, p -value=0.009), gynecological care,

Table 2

Association of bisphosphonate treatment discontinuation within 1 year with defined variables: Cox regression analyses.

Outcome variables	Hazard ratio ^a (95%CI)	p -Value
Age ≥ 70 versus < 70	0.78 (0.67–0.91)	0.001
West Germany versus East Germany	2.01 (1.60–2.52)	< 0.001
Private health versus statutory health insurance coverage	1.32 (1.07–1.62)	0.009
Chemotherapy	0.74 (0.63–0.87)	< 0.001
Hormone therapy	0.68 (0.57–0.80)	< 0.001
Pain medication	0.70 (0.59–0.82)	< 0.001
Number of different drugs taken per day	0.83 (0.78–0.89)	< 0.001
Gynecologist treatment versus GP treatment	0.83 (0.71–0.98)	0.024
Intravenous versus oral bisphosphonates	1.00 (0.85–1.17)	0.997
Depression	0.97 (0.82–1.15)	0.745
Antidepressants	0.94 (0.77–1.15)	0.550

^a Discontinuation of therapy adjusted for age, region (west Germany), urban residency, gynecologist care, health insurance coverage (private), and all variables in the model.

chemotherapy, endocrine treatment, pain medications, and the number of drugs taken per day decreased the risk of treatment discontinuation (HR=0.83, 95% CI: 0.71–0.98, HR=0.74, 95% CI: 0.63–0.87; HR=0.68, 95% CI: 0.57–0.80; HR=0.70, 95% CI: 0.59–0.82; and HR=0.83, 95% CI: 0.78–0.89, respectively; all p -values lower than 0.024). By contrast, BIS type (intravenous/oral), depression, and the use of antidepressants did not significantly impact treatment persistence.

4. Discussion

In our study, we were able to demonstrate that women aged ≥ 70 discontinued their BIS treatment less frequently than women aged < 70 years during the one-year follow-up period. In addition, we showed that residing in West Germany and having private health insurance coverage increased the risk of therapy discontinuation, whereas age, gynecological care, chemotherapy, endocrine treatment, pain medications, and the number of drugs taken per day decreased this risk.

BC is a cancer that is frequently associated with metastases, particularly bone metastases. These malignant bone diseases have a negative impact on the balance between bone formation and resorption [12]. Although BIS are one component of the standard recommended treatment for women with BC and bone metastases, both their safety and their efficacy profile need to be taken into account. Thus, therapy persistence is of the utmost importance in achieving the optimal outcome as observed in RCTs.

Nonetheless, treatment discontinuation rates are high, reaching 50% in patients with chronic diseases. One of the major factors impacting treatment discontinuation in women with BC is age [11,17]. On the basis of their study in 2003 including 2378 postmenopausal women with BC from New Jersey, Partridge et al. demonstrated that both patients aged < 45 and > 85 were at a higher risk of therapy discontinuation [18]. He and his colleagues recently corroborated these results in 3395 women with BC from Sweden, since women < 40 and > 65 had a higher likelihood of treatment discontinuation [19]. There are several hypotheses that may explain this non-linear, complex relationship between therapy persistence and age. It is known that older women are more commonly affected by BC than younger women and thus tend to adjust better to this chronic disease [20–22]. Since the prognosis for younger women with BC is worse on average than that for older women with the disease, their poor compliance and persistence is of particular concern [23]. By contrast, patients aged > 80 usually suffer from multiple diseases and insufficient social/familial support, leading to a decrease in treatment compliance and persistence [18,24]. Interestingly, several studies have also demonstrated that persistence with BIS therapy increases with age [25,26]. In their 2005 study comprising 2124 postmenopausal women treated with alendronate, etidronate, or risedronate, Penning-van Beest and colleagues found that BIS persistence was higher in patients aged between 65 and 69 and between 70 and 74 than in patients aged between 55 and 59 [25]. Three years later, Gallagher et al. showed in 44,531 patients treated with oral BIS that patients aged > 60 exhibit higher compliance and persistence rates than patients < 60 [26]. Therefore, our findings are in line with these reports and demonstrate that age positively impacts BIS treatment persistence in women with BC and bone metastases.

Our study also showed that the risk of treatment discontinuation is lower in patients treated in gynecological practices than in those receiving treatment in general practices. In this context, it is worth mentioning that in Germany, gynecologists are customarily responsible for the treatment and management of women with BC. Interestingly, chemotherapy, endocrine treatment, pain medications, and the number of drugs served in preventing

discontinuation. This result is not in line with those of He et al., who recently reported that the number of medications decreased persistence with endocrine treatment in BC patients [19]. Nonetheless, there are two important differences in our study. We did not analyze persistence with endocrine treatment, rather, we focused on BIS therapy and also only included women with BC and bone metastases. It is possible that the follow-up of patients with high numbers of treatments was more specific than the follow-up of patients with lower numbers of medications.

Residing in West Germany also decreased BIS persistence. In 2015, Jacob et al. demonstrated in 4,915 BC women that the treatment discontinuation rate is higher in West Germany than in East Germany [1]. Finally, our study returned one outcome that requires careful discussion: we found that private health insurance increased the risk of treatment discontinuation. This finding may cause confusion since women with private health insurance coverage are usually wealthier than those with statutory insurance coverage. Although patients who subscribe to a private health insurance plan may benefit from better medical treatment and management, one must consider the fact that these patients may display risk factors for therapy disruption not present or less present in other patients.

This study was subject to several limitations, one of which is that the population included was not selected specifically by age and therefore the proportion of elderly women was relatively small. Consequently, we were only able to differentiate between two different age groups (< 70 and ≥ 70). Nevertheless, we believe that as the age range in our study population is in concordance with the age range of the majority of people with BC among the general population, it therefore does not introduce a selection bias. In addition, the database did not include any valid information on TNM classification. Furthermore, no detailed documentation of treatment side effects was available. Data on socioeconomic status and lifestyle-related risk factors were also unavailable.

Women aged ≥ 70 with BC and bone metastases were at a lower risk of BIS treatment discontinuation than women < 70. Further studies are required to gain a better understanding of the non-linear, complex relationship between age and treatment persistence.

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