Oncological Diseases and the Use of Bisphosphonates: A Cross-sectional Study in Bulgaria and the Plovdiv Region

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Abstract

Introduction: Bisphosphonates (BPs) are some of the most commonly used drugs for treating oncology patients with multiple myeloma or bone metastases. In recent years, cases of bisphosphonate-associated osteonecrosis of the jaws (BAONJ) have been increasingly reported in oncology patients on intravenous BPs.

Objective: To study the patients with oncological diseases in Bulgaria and in the Plovdiv region and the application of intravenous BPs in patients with malignancies in the Plovdiv region.

Material and Methods: A cross-sectional study was conducted, using as a primary source of information the official publications of the Bulgarian National Cancer Registry (NCR) from 2012 to 2016. Additional information was obtained from hospitals’ pharmacy wards located in Plovdiv region, where BP therapy was administrated during the same 5-year period. Data processing and analysis were accomplished using SPSS statistical software (SPSS for Windows, version 24, Armonk, NY: IBM Corp). A p-value <0.05 was considered statistically significant. Time series analysis was applied to study the annual data, obtained from NCR.

Results: In Bulgaria and in Plovdiv, the time series analysis demonstrated a positive trend for the total number of cancer cases, with a significantly higher proportion of women (Bulgaria (z=103.6, p<0.05), Plovdiv (z=45.9, p<0.05)). However, for the period, in the newly registered cancer cases we observed higher proportion of men (Bulgaria (z=10.6, p<0.05), Plovdiv (z=4.7, p<0.05)). The most frequent localization of malignant formations are: skin, mammary gland, female reproductive organs, gastrointestinal tract, and respiratory tract. In Plovdiv, on average, 2.3% of oncology patients received BPs, with a higher proportion of women (52%, n=402; z=1.6, p=0.117). Zoledronic acid is the most commonly used BP.

Conclusion: The increasing trend of oncology patients potentially expands the treatment with BPs with possible subsequent development of BAONJ.

Keywords: cancer, oncology, trends, bisphosphonates, osteonecrosis, jaw

1. INTRODUCTION

The distribution of oncological diseases has a serious impact on the healthcare system. In addition to the direct invasive treatment of the malignant process, a large proportion of patients are receiving therapy with various types of drugs, one of which are the Bisphosphonates (BPs). They bind to the hydroxyapatite in the bone and inhibit osteoclast-mediated bone resorption [1]. In clinical practice, BPs have been used for several decades to treat multiple myeloma, osteolytic bone metastases, osteoporosis, Paget disease, fibrous dysplasia, hypercalcaemia of tumor origin, etc. [2–4]. In recent years, reports of Bisphosphonate-associated osteonecrosis of the jaw (BAONJ) have been increasingly reported in patients treated with BPs. These are patients diagnosed with various oncological diseases: breast cancer, prostate cancer, lung cancer, and multiple myeloma, on intravenous BPs treatment. Although, in the current clinical practice an informed consent is required, patients are still not familiar with the risk of BAONJ as a serious adverse event of the treatment. Moreover, there
is not an explicit line of action considering: (1) consultation with a dental specialist for risk assessment; (2) potential need for dental examination before starting the treatment; (3) follow-up and timely treatment during the BPs administration period. This is an extremely complex and multifactorial process requiring monitoring and an individual approach to each patient, and efforts should be directed primarily towards the prevention of BAONJ both before and after initiation of BP therapy.

The aim of this research is to study the patients with oncological diseases in Bulgaria and in the Plovdiv region and the application of intravenous BPs in patients with malignancies in the Plovdiv region.

2. MATERIALS AND METHODS

A cross-sectional study was conducted, using as a primary source of information the official publications of the Bulgarian National Cancer Registry (NCR) from 2012 to 2016 (5-year period). The variables studied were: age and gender of patients with neoplasms and newly discovered neoplasms. Additional information was obtained from hospitals’ pharmacy wards located in Plovdiv region, where BP therapy was administrated during the same 5-year period. The variables included were: age, gender, type of BP, number I.V. administrations. Continuous variables were expressed as mean±standard deviation (SD), or by median (25th, 75th percentiles), based on normality of data. Difference between averages (medians) was proved by applying two-sample t-test (Mann-Whitney U test), based on the data distribution. Categorical variables were expressed as counts or percentages. Difference between two proportions was analysed by z-test.

Data processing and analysis were accomplished using SPSS statistical software (SPSS for Windows, version 24, Armonk, NY: IBM Corp). A p-value <0.05 was considered statistically significant. Time series analysis was applied to study the annual data, obtained from NCR.

3. RESULTS

In Bulgaria, for the period 2012-2016, an average of 279 421 neoplasms per year have been registered, with an increasing trend (Figure 1). A significantly higher proportion of women was found (z=103.6, p<0.05) (60%, n=167 950).
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Figure 3. Time series analysis and trend of all registered oncological diseases in Plovdiv region for a 5-year period

Newly registered cases in the region are an average of 3,399 (10% of average total reported for Plovdiv region), with a decreasing tendency of the number of cases (Figure 4). On average, the newly registered males were 1,819 (54%) and the females were 1,580 (46%), with an increase in the number of men, a decrease in the number of women, and a significantly higher proportion of men (z=4.7, p<0.05).

Figure 4. Time series analysis and trend of newly registered oncological diseases in Plovdiv region for a 5-year period

In Bulgaria, and in the Plovdiv region, the averagely most common localizations of malignancy for the 5-year period are: skin (63,816 (15%) / 9,106 (18%)), mammary gland (50,549 (12%) / 5,927 (12%)), female reproductive organs (82,604 (19%) / 7,779 (15%)), gastrointestinal tract (81,090 (19%) / 9,029 (18%)), and respiratory tract (30,005 (7%) / 4,245 (8%)). There was also an increase in breast cancer and prostate cancer cases. These types of cancer are frequently linked to the development of bone metastases and the need of subsequent BP treatment.

For the period, in the Plovdiv region, an average of 766 (2.3%) of cancer patients received BPs (Table 1), with a higher proportion of women (52%, n=402; z=1.6, p=0.117) and a median age of 66 yrs. (58 yrs., 73 yrs.).

Table 1. Distribution of oncology patients from Plovdiv, receiving intravenous BPs by year for the period 2012 – 2016

| Year | Number of cancer patients | Cancer patients, receiving I.V. BP |
|------|--------------------------|----------------------------------|
|      | n                        | %                                |
| 2012 | 34031                    | 705                              |
| 2013 | 32307                    | 738                              |
| 2014 | 32666                    | 893                              |
| 2015 | 33173                    | 732                              |
| 2016 | 34025                    | 763                              |

I.V. = intravenous, BP = Bisphosphonates

Zoledronic acid (ZA) was the BP administered in 3801 (99%) of cases for the overall 5-year period. BPs were mostly used in patient with breast cancer (13%, n=99), onco-hematological diseases (19%, n=150), prostate (5%, n=43) and lung cancer (4%, n=29) (averages for the period). There was a decline in the median number of applications of BPs from an average of 5 (2012-2014) to 3 per year in 2015 and 2016, with women receiving more infusions than men (Man-Whitney U, p<0.0001).

4. DISCUSSION

BPs are effective in the treatment of diseases with high bone resorption. The largest group of patients receiving BP therapy are those with oncological diseases. The increasing number of patients with malignancies results in more frequent use of BPs. Thus, in recent years, substantial number of patients had been diagnosed with BAONJ, which, according to some authors, is due to the significantly higher total doses and duration of intravenous therapy with BPs [1, 5].

Regarding the incidence of neoplasms, in 2012 Bulgaria occupies the 43rd place in the world [6] with a total of 270,492 registered patients. Globally, in 2012, there are 14 million new cases of cancer. The number of new cases is expected to increase to 22 million over the next two decades. More than 60% of new oncology cases worldwide are seen in Africa, Asia and Central and South America [7]. The global trend of increasing number of patients with cancer is also noticeable in Bulgaria.
In the US, approximately 39.6% of men and women will be diagnosed with a malignancy at some point in their lives (based on data from 2010-2012), with 1685210 new cases of cancer [8]. Europe accounts for only one-eighth of the world's population, but there are about a quarter of all cases of cancer with about 3.7 million new patients per year [9]. In 2012, there were about 3.45 million new cases of neoplasms in the European Union, with the number of newly registered men being higher than that of women [10]. In Bulgaria, and in the Plovdiv region, for the 5-year period, we have seen the same gender distribution of newly registered neoplasms.

Globally, in 2012, more than 4 out of 10 new cases of neoplasms are localized in the lungs, mammary glands, colorectal area, or prostate. These 4 types of cancer account for 52% of all newly registered oncological diseases in the UK in 2014 [11].

As for the frequency of prescription, more than 2.5 million patients worldwide have been treated with BPs [12]. Almost 2 million people receive this treatment as part of cancer therapy [13]. Nowadays the numbers are constantly increasing.

The percentage of women on BP therapy in our study is higher. This trend can be explained by the fact that breast cancer is the most common type of cancer, which may require potential therapy with these drugs. In Germany, BF was the therapy administered to 9.6% of the overall patients with breast cancer [14].

We found that the most common type of BP used on cancer patients is Zoledronic acid (ZA). ZA is the most effective agent from the BP group in terms of reducing skeletal involvement in multiple myeloma, as well as a wide range of solid tumors affecting the bones by 30-50% [15]. However, ZA is considered to have the highest risk of possible BP complications and has the highest potency measured [16]. This type of BP causes most of the cases of BAONJ [5,16,17,17,19,20,21,22]. In patients with breast cancer in Germany, ZA is also the most commonly used BP for the prevention of bone metastases [14]. In Texas (USA) 2/3 of patients with breast cancer receive ZA [23].

The median age of patients receiving BPs in our study coincides with the results reported in studies from five European countries (France, Germany, Italy, Spain, UK). The mean age of the patients in each group of malignancies (solid tumors - ST and oncohematological diseases - OHD) is close (CT: 67.7 yrs., OHD: 67.5 yrs.). From patients with ST, the youngest has German origin (62.6 yrs.) and the oldest registered in Italy (70.3 yrs.). The mean age of patients with OHD is similar in different countries and ranges from 64.3 yrs. to 68.3 yrs. [24].

In line with other studies, our results detected that the most common types of malignancies in patients receiving BP therapy in the Plovdiv region are breast cancer, prostate cancer, lung cancer and multiple myeloma [24,25,26,27].

In the last two years of our study, the median number of applications of BPs start to reduce in association with initiated changes in the clinical practice: BPs are not administered every 3/4 weeks as initially recommended, but every 3 months [20,28,29] or even every 6 months [28]. Optimized dosing frequencies of bisphosphonates administration has resulted in less reported severe adverse events [16]. According to the American National Anti-Neoplasm Network, there have been no BAONJ cases in bone loss prevention studies with ZA administrated every 6 months [30].

5. CONCLUSIONS

The results of the study show an increase in patients with oncologic diseases, especially the types that metastasize to the bones and need subsequent bisphosphonate treatment, and therefore a potential increase of BAONJ is expected. Our efforts should be directed to improve the communication between healthcare practitioners and patients to facilitate the management of BAONJ. Further research is required to identify the preventive measures and flexible treatment protocols, adapted to the individual patient, giving priority to patients' quality of life.

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CONFLICTS OF INTEREST

There are no conflicts of interest to disclose.
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