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Patients' Awareness of the Complications of Bisphosphonate Therapy

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Abstract

INTRODUCTION: Bisphosphonate-associated osteonecrosis of the jaws (BAONJ) is a serious complication that has been reported predominantly in cancer patients treated with Bisphosphonate (BP). The level of knowledge of dental and medical practitioners, as well as patients, is crucial for its prevention.

OBJECTIVES: To investigate patients' awareness of BAONJ in order to evaluate some problems of the prevention, prophylaxis and diagnosis.

MATERIALS AND METHODS: A prospective epidemiological study of 112 oncology patients diagnosed with Bisphosphonate-associated osteonecrosis of the jaw was conducted in the Clinic of maxillo-facial surgery of university multiprofile hospital for active treatment (UMHAT) "St. George", Plovdiv, Bulgaria, based on anamnesis, clinical examination, hospital documentation, and imaging studies. SPSS Statistics v.24 was used for statistical analysis, at a significance level $p<0.05$.

RESULTS: Before initiation of therapy, only 17.86% of the patients were consulted by a medical practitioner about the risk of jaw complications associated with the use of Bisphosphonates, 9.82% knew about the need for regular dental check-ups after the initiation of therapy and 4.46% had a dental examination and oral sanation. By the time of diagnosis, 61.61% of the patients remained unaware, with the last dental manipulation being most often extraction (52.68%) and removable dentures (21.42%) considered risky by experts. Diagnosed by a general dental practitioner or oncologist were 6.74% of the respondents – the medical practitioners who usually monitor the condition of these patients. Over 2/3 of the patients were diagnosed at a more advanced stage (II/III).

CONCLUSION: The lack of patient awareness leads to omissions and errors in their prophylaxis, and to the diagnosis of BAONJ at a more advanced stage.

KEYWORDS: bisphosphonates; osteonecrosis; prevention; awareness; patients

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Introduction

Bisphosphonates (BP) are pyrophosphate analogs that bind to hydroxyapatite crystals in the bone structures and slow the process of osteoclastic bone resorption through decreasing osteoclast activity by suppressing progenitor development and recruitment and inducing osteoclast apoptosis [1,2]. In clinical practice, BP has been used for the treatment of different conditions affecting the bone structures such as multiple myeloma, osteolytic bone metastases, osteoporosis, Paget's

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disease, fibrous dysplasia, McCune-Albright syndrome, and others [2,3]. In recent years, many scientists and clinicians have reported a complication following the intake of this drug, called Bisphosphonate-associated osteonecrosis of the jaw (BAONJ), which mainly occurs in cancer patients receiving intravenous BP treatment. There are many discussions and debates regarding the different aspects of this complication, from the definition and risk factors to the clinical manifestations and different methods of treatment and prevention. It is evident that this extremely complex and multifactorial process requires careful monitoring and an individual approach to each patient [3]. Efforts should be focused primarily on its prevention, both before and after the start of the treatment, as the condition causes irreversible changes in the patient's dental health and overall health. Awareness of the problem of dentists, oncologists, and patients and their willingness to work together to reduce risk is crucial. Patients should be informed about the complication before starting therapy, sanitized if necessary, as well as prophylaxed before and during BP therapy.

The aim of this study is to investigate the awareness of the complication of BP therapy of patients diagnosed with BAONJ in order to evaluate some problems of the prevention, prophylaxis, and diagnosis.

Material and Methods

A prospective epidemiological study of 112 oncology patients diagnosed with Bisphosphonate-associated Osteonecrosis of the jaw in 2016 and 2017 was conducted in the Clinic of maxillo-facial surgery of UMHAT "St. George", Plovdiv, Bulgaria, based on anamnesis, clinical examination, hospital documentation, and others. The data is reflected in à specially created for the purpose epidemiological study card. For descriptive statistics, continuous variables were displayed as the median and interquartile range (median ± IQR) and categorical variables as counts and percentages. Variables were compared with the use of two proportions z-test and Pearson's chi-square. All statistical analyses were performed with SPSS version 24 (IBM Corporation, New York, NY). A p-value below 0.05 was considered statistically significant.

This study, as a part of a dissertation, titled "Bisphosphonate-associated Osteonecrosis of the Jaws - Epidemiological and Clinical Research" was submitted to the Ethical Committee of the Medical University of Plovdiv with ID number P-3911 (29.05.2018) and approved with protocol No.4/28.06.2018.

Results

The median age of patients was 68 years (IQR = 16), with a minimum of 38 years and a maximum of 85 years. There was no statistically significant difference between the relative proportions of men (51.79%, n = 58) and women (48.21%, n = 54) (p> 0.05).

Breast cancer (40.18%, n = 45) and prostate cancer (37.71%, n = 40) (p> 0.05) were leading oncological diagnoses. Of all patients studied, 16.07% (n = 18) had another type of cancer, most commonly renal cell carcinoma (n = 9) (Figure 1).

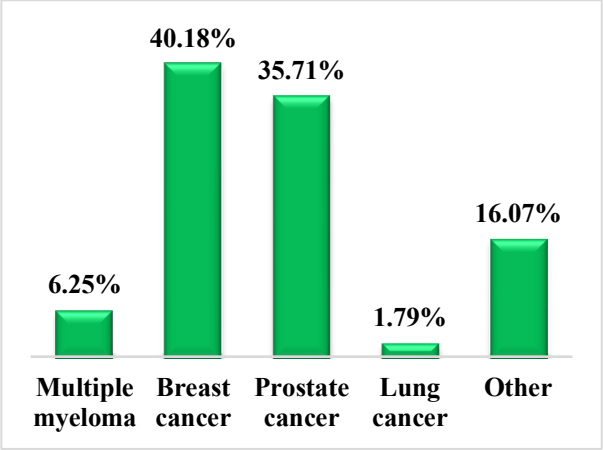

Figure 1. *Type of cancer of the studied patients.*

Only 17.86% (n = 20) of patients were consulted by a physician about the risk of jaw complications associated with Bp administration prior to initiating therapy. Also, the need for regular dental examinations after starting therapy has been explained to just 9.82% (n = 11). Even more worrying is that only 4.46% (n = 5) underwent a prophylactic dental examination and, if needed, treatment of dental problems before

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the start of the treatment, and the same small proportion of patients were asked by the physicians prescribing BP therapy if they had performed such an examination. before initiating BP therapy, which indicates a low awareness of medical professionals about BAONJ.

There was an association between the type of cancer and the presence of consultation by a physician about the risk of jaw complications prior to the start of BP therapy ($\chi2 = 15.32$, $p < 0.05$), the presence of an explained need for regular dental check-ups ($\chi2 = 19.76$, $p < 0.05$), the performed prophylactic dental examination and potential oral sanation ($\chi2 = 26.01$, $p < 0.05$) and the request from the attending physician before starting BP therapy for consultation / examination by a dentist ($\chi2 = 26.01$, $p < 0.05$), as patients with multiple myeloma were better informed than patients with all other oncological diagnoses.

When asked about the first source of information on the risk of maxillary complications associated with the use of BP, the largest proportion of patients (61.61%, n = 69) indicated that they were completely uninformed before diagnosis and that their first explanation of the problem was received by a specialist in the Clinic of maxillo-facial surgery. The ones who received the information from the treating physicians and who found out about BAONJ from a friend or another patient had equal relative frequency (11.61%, n = 11). With the same low proportion of 2.68% (n = 3) were the patients who indicated a dentist, medical leaflets, or the Internet as the primary source, and only 1 patient received information on the problem from their general practitioner, none - from the media. These results once again show the low level of awareness of many practitioners on the problem (Figure 2).

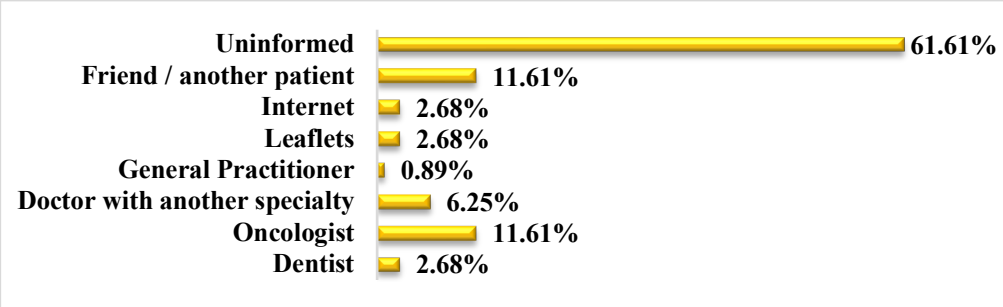

Figure 2. *Distribution of patients according to the first source of information on the risk of jaw complications associated with the application of BP.*

A statistical association was found between the type of cancer and the primary source of information for patients with BAONJ ($\chi2 = 45.31$, $p < 0.05$), where patients with multiple myeloma, most often consulted by a physician in another specialty (hematologist), were significantly more than those with breast cancer. Additionally, in those uninformed at the time of the study, patients with mammary carcinoma were with significantly higher proportion than those with multiple myeloma.

Both before and after starting BP therapy, on average, over half of the patients visited a dentist once a year. Positively, but unsatisfactorily, the proportion of those with dental examinations less than once a year decreased from 38.39% (n = 43) before the start of BP therapy to 26.79% (n = 30) after, at the expense of an increasing number of patients visiting the dental office semi-annually and quarterly, but these percentages are still lower than desired. The fact that patients who do not visit a dentist increased slightly from 0.89% (n = 1) to 2.26% (n = 3) can be explained by the fact that the period of treatment is much shorter than the period before its initiation (Figure 3).

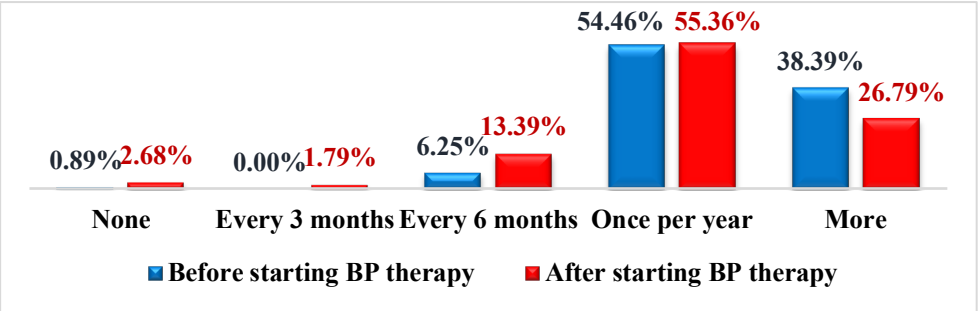

Figure 3. *Distribution of the frequency of visits to the dentist before and after the start of BP therapy.*

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Half of the studied patients were diagnosed at stage II of BAONJ (according to AAOMS) (50.89%, n = 57). Significantly less were at stage I (29.46%, n = 33) (p <0.05), followed by 17.86% (n = 20) at stage III. Only 2 (1.79%) patients were at stage 0 at hospitalization, indicating a lack of prevention and monitoring.

Most of the patients were diagnosed during the 2-year period of the study (79.46%, n = 89), while 23 (20.54%) were diagnosed with BAONJ before. In more than ¾ of cases, the patients were diagnosed by a specialist from the clinic of maxillofacial surgery (76.79%, n = 86), followed by 15.18% (n = 17), whose diagnosis was made by an oral surgeon in a specialized dental practice. Low equal shares of patients were diagnosed by a dentist with another specialty or by an oncologist (3.57%, n = 4), while no patients were diagnosed by their general practitioner, showing low awareness of these medical practitioners on the problem (Figure 4).

Tooth extraction was the last dental procedure in more than half of the patients (52.68%, n = 59), followed by the placement of removable dentures (21.42%, n = 24). These two manipulations are most often cited as risky for the emergence of BAONJ and again show the low awareness of dentists and patients themselves about the prevention of the problem (Figure 5).

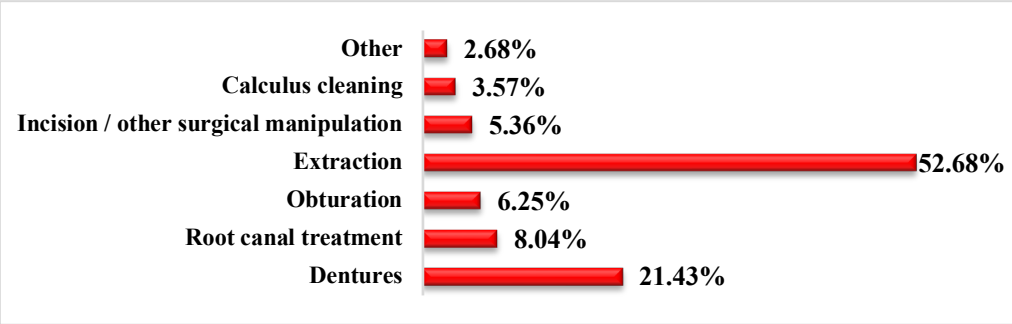

Figure 5. *Last dental procedure before the onset of symptoms / diagnosis of BAONJ.*

Discussion

The level of awareness of medical specialists and patients about the problem is crucial for the prevention of BAONJ. Our study showed not only extremely low awareness of patients with BAONJ, but also indirectly of the medical and dental specialist, treating these patients. A low level of knowledge about the problem has been found in our previous survey [3], as well as other studies on the awareness of physicians and dentists about the complication [4-10].

Similar to the low patient awareness in our study, in a clinical trial of BP therapy patient awareness of prophylaxis with these medications, all subjects reported not receiving instructions for good oral hygiene [11].

A survey found that only 12.4% of participants were aware about the risk of jaw osteonecrosis following BP use, and only one third of them has received information from their prescribing physicians. Moreover, just 5% were referred to a dentist for screening prior to initiating BP treatment. Patients receiving IV BP

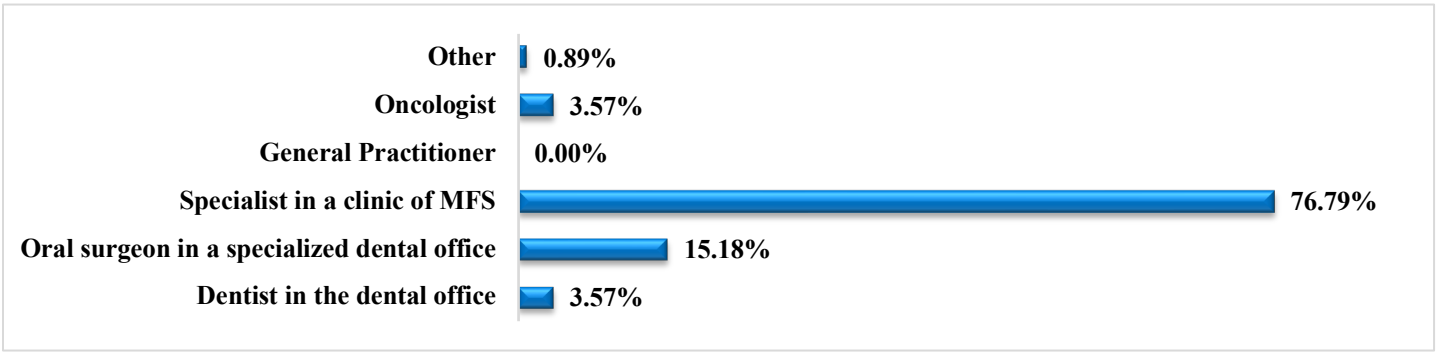

Figure 4. *Distribution of physicians, who diagnosed by BAONJ, by their specialty.*

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and those with a university-level education had better awareness about the potential risk than oral BP users and those with a high school education level [12].

Other study on the problem showed that just 1/3 of patients were aware about the risk. Patient knowledge was obtained primarily from one of the following sources: physicians (n = 6), physician assistants (n = 1), nurses (n = 1), dentists (n = 2), or the patients themselves (n = 1). Females were better informed about the complications than males. The awareness among the subjects with education at college level appears to be higher than the subjects having education less than high school level. Even though, a dental check- up, is mandatory, prior to starting these medications, to see if any dental treatment is required, only slightly more than half of the patients (54.72%) had a dental checkup [13].

To date, there is no evidence-based unified therapeutic strategy for BAONJ and the condition is considered irreversible, so the focus of the medical community is on the possibilities for its prevention [14-16]. The aim is to minimize the risk of development of this complication:

Before the start of bisphosphonate therapy

It is the responsibility of the physicians prescribing BP to provide patients who are about to initiate therapy with them or another antiresorptive agent with adequate information regarding the risk of developing BAONJ and to refer them for a comprehensive dental examination before starting therapy [16]. Dental care should be performed by a dental professional (dentist and oral/ maxillofacial surgeon) who is familiar with anti-cancer therapies and their expected adverse effects and is committed to integrating oral care in the treatment of cancer [17]. Responsibility of the dentist is to apply preventive measures and inform patients about the need to continue regular dental check-ups during treatment with antiresorptive agents.

Patients should be informed that a significant risk of developing BAONJ remains, despite the adoption of specific prevention protocols. The reason is that the condition can develop in the absence of dental trauma or infection, and also because there are a number of minor factors that cannot be easily controlled (e.g. trauma to areas of the thin mucosa). Patients should be alerted to the possible clinical manifestations and symptoms of BAONJ and instructed to report their complaints in a timely manner to the oncologist / dentist and in order for them to make a final diagnosis [15,18].

The American Association of Clinical Oncology (ASCO), the American Association of Oral and Maxillofacial Surgeons (AAOMS), the International Task Force on Osteonecrosis of the Jaw, and the European Medicines Agency (EMA) recommend that all patients undergo a comprehensive dental examination and preventive therapy before initiating therapy with an antiresorptive agent or angiogenesis inhibitor [19-23].

The assessment includes [19]:

• Unsavable teeth and those that are unlikely to be saved must be extracted. If systemic conditions allow, initiation of therapy with an antiresorptive or antiangiogenic agent should be delayed until the extraction site has healed (14 to 21 days) or until there is sufficient bone formation/healing. These decisions must be made jointly by the attending physician and the dentist;

• When possible, less invasive dental procedures with preservation of the tooth root are preferred to tooth extraction;

• Active oral infections must be treated, and objects at high risk of infection must be removed;

• Dental prophylaxis, caries control, and conservative restorative dentistry are critical to maintaining functionally healthy dentition;

• Patients with full or partial dentures should be examined for areas of mucosal trauma;

• Patients should be trained in the importance of dental hygiene and regular dental examinations and assessment of dental status and instructed to report any pain,

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swelling, or bone exposure immediately [19].

The implementation of dental screening and appropriate dental treatment measures prior to initiating antiresorptive therapy reduced the risk of BAONJ in several prospective studies compared retrospectively to patients who did not have dental prophylaxis [24-26].

Pechalova *et al.* [27] recommend:

• A thorough clinical examination of the dentition and oral cavity, panoramic radiograph and, by the discretion of the doctor, targeted periapical radiographs as a mandatory re-quired minimum

• Conducting dental treatment aimed at elimination of infection and the need for invasive procedures in the short- and mid-term future.

• All invasive dental procedures should be performed at least one month before initiating bisphosphonate therapy in order to allow sufficient time for recovery of the jawbone. Restoration with dental implants is not recommended.

After the start of bisphosphonate therapy

Patients should go to preventive examinations - every three/four months, with additional imaging studies to monitor for osteolysis, osteosclerosis, periodontal dilation and involvement of the furcations [27].

Oral hygiene should be carefully monitored, patients should maintain excellent oral hygiene (with toothpaste and toothbrush, flossing, and antiseptic mouth wash) to reduce the level of periodontal and oral infection, and to avoid invasive dental procedures, if possible. In this regard, smoking cessation is recommended [16].

Patients should be asked about any planned dental procedures before administering each dose of antiresorptive agent and reminded to avoid invasive ones (tooth extraction, implants, and all other procedures that involve manipulation of the jawbone or periosteum) while being treated with these drugs. They need to make sure that relatively non-invasive dental procedures such as professional cleaning, cavity maintenance and even routine root canal treatments do not increase the risk of BAONJ and can be safely performed based on treatment protocols used for the general population. Dental crowns may be placed. Removable dentures should be carefully planned in areas of expected excessive pressure, preferring soft plastic constructions [28].

It remains unclear whether less frequent use of zoledronic acid reduces the incidence of BAONJ. A retrospective analysis indicates a reduced percentage of patients with multiple myeloma who received zoledronic acid every 12 weeks instead of every four weeks [29].

Randomized trials mainly in breast and prostate cancer populations did not report a significantly lower percentage of osteonecrosis cases with BP intake at long intervals [30].

Discontinuation of BP therapy prior to invasive dental procedures (e.g. tooth extraction, implant placement, or apical endodontic treatment) during treatment with an antiresorptive agent or antiangiogenic agent has not been proven effective and there is scarce data to guide the physician in this direction [16].

Conclusions

BAONJ is a complication associated with BP intake that severely impairs the quality of life of many patients. As the condition is considered irreversible and treatment options are still a complex and controversial issue among clinicians, our efforts should be focused mainly on its prevention both before and after the initiation of BP therapy. Knowledge of epidemiology and risk factors is key. It is crucial to raise the awareness of dentists, oncologists, and patients and their willingness to work together as a team to reduce the risk of developing this complication. Educational programs should be included in the qualification of physicians prescribing and treating patients with BP, dental practitioners who can have such patients in their everyday practice, as well as in the consultation of patients taking this type of medication.

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Authors' Contribution

Author 1 conceived and designed the analysis, collected the data, performed the analysis, and wrote the paper.

Author 2 designed the analysis, collected the data, and proofread the manuscript.

Author 3 performed the statistical analysis and proofread the manuscript.

Conflicts of Interest Statement

There is no conflict of interest to disclose.

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