ABSTRACT

**Purpose:** To investigate patient diagnosed with BAONJ in order to identify the presence of risk factors.

**Material/Methods:** A prospective epidemiological study of 112 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 imaging studies. SPSS Statistics v.24 was used for statistical analysis, at a significance level $p<0.05$.

**Results:** Of the patients, 77.89% had a primary oncological diagnosis of breast or prostate cancer; the average duration of bisphosphonate therapy up to the time of the study is 4.5 years; the most common co-morbidities were hypertension (72.73%), anemia (40.00%) and diabetes (23.67%); 65.18% of patients smoke or are former smokers; the time till first oral complaints after initiation of BP treatment was usually 2 years (31.25%, $n = 35$) and 3 years (24.11%, $n = 27$) ($p > 0.05$); the last dental manipulation before the onset of symptoms was tooth extraction (52.68%), followed by removable dentures (21.42%).

**Conclusions:** The investigation of identified in the literature risk factors with their occurrence in the studied population shows a correlation with the data of leading researchers.

**Keywords:** bisphosphonates, Osteonecrosis, risk factors, oncology, epidemiology,

INTRODUCTION

Bisphosphonates (BP) are synthetic analogs of naturally occurring pyrophosphate compounds with high affinity to calcium crystals, which allows them to bind to bone hydroxyapatite and inhibit osteoclast-mediated cross-resorption [1]. In the clinical practice, BP have been used for several decades for the treatment of multiple myeloma, bone metastases, osteoporosis, Paget disease and others. In recent years, reports of Bisphosphonate-associated Osteonecrosis of the jaws (BAONJ) have increased[1]. One of the most discussed and controversial aspects of this complication are the risk factors, which are most commonly associated with bisphosphonate therapy, dental treatment, concomitant illness and harmful habits. This suggests that BAONJ is an extremely complex and multifactorial process requiring careful monitoring and individual approach to each patient[1]. The aim of this study is to investigate patient diagnosed with BAONJ in order to identify the presence of risk factors.

MATERIAL AND METHODS

A prospective epidemiological study of 112 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 imaging studies. The data is reflected in a 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.

RESULTS

The median age of the patients was 68 years (IQR = 16), with no statistically significant difference between the relative parts of men (51.79%, $n = 58$) and women (48.21%, $n = 54$) ($p > 0.05$). The mean duration of BP therapy of patients with BAONJ at the time of the study was 4.5 years, with Zoledronic acid at a dose of 4 mg. In 97.32% ($n = 109$) of cases, the therapy was carried out according to a standard monthly schedule, with periods
Breast cancer (40.18%, n = 45) and prostate cancer (37.71%, n = 40) (p > 0.05) were the leading oncological diseases in patients with BAONJ, coinciding with specialist data. Of all patients, 16.07% (n = 18) had another oncological diagnosis, most commonly renal cancer (n = 9). (Figure 1)

**Fig. 1.** Type of cancer in the studied patients with BAONJ

Of the co-morbidities, hypertension (72.73%, n = 80) was the most common, which we associate with the age of patents, as a statistically significant association between age and co-morbidities was found ($\chi^2 = 56.58$, p < 0.05). Anemia was found in 40.00% (n = 44) of patents, and 1/4 had diabetes, which, according to the literature, are considered risk factors for the development of the complication. (Figure 2)

**Fig. 2.** Concomitant diseases/conditions in the studied patients with BAONJ

Nearly 1/3 of patients received anti-angiogenic agents and 22.73% (n = 25) corticosteroids, considered at risk for BAONJ. The highest relative part of 67.27% (n = 74) were those receiving other drugs, mainly for the treatment of hypertension, various cardiovascular diseases, as well as hormone and insulin therapy, rarely associated with the complication. (Figure 3) Over 2/3 of the patients were smokers (40.18%, n = 45) or ex-smokers (25.00%, n = 28).
The time till onset of first complaints in the oral cavity after initiation of BP therapy was most often 2 years (31.25%, n = 35), and 3 years (24.11%, n = 27) (p > 0.05). (Figure 4)

**Fig. 4.** Time till first oral complaints after initiation of BP treatment

The last dental manipulation before the onset of symptoms was tooth extraction (52.68%, n = 59), followed by the placement of removable dentures (21.43%, n = 24). These two manipulations are most often considered risky by specialists. Patients whose most recent dental manipulation was root treatment, obturation, incision, tartar cleaning, and others were with lower relative shares, as these types of dental treatment are rarely associated with the emergence of BAONJ. (Figure 5)
DISCUSSION

The risk factors considered by other authors and we can be classified into the following groups:

1. Risk factors related to the medication

Scientific evidence supports the prevailing view that the use of Zoledronic acid (ZA) carries the highest risk [2, 3, 4, 5, 6]. Increasing the total dose and the intravenous administration of BP also carry a higher risk of developing osteonecrosis [3, 4, 5, 6, 7]. These data correlate with the fact that in the present study, all patients received ZA intravenously, at the same standard dose.

The frequency of administration has also been recognized as a risk factor by many oncologists, who now prescribe intravenous ZA every 3 or 6 months, which differs from the manufacturer’s recommendations for administration every 3 weeks to a month. This reduction in the frequency of administration leads to an observed decrease in the number and severity of cases [6].

The incidence of BAONJ is higher with longer treatment duration, especially when treatment exceeds four years. Some authors have found that the median exposure period in patients with BAONJ is 39 months (from 11 to 86 months), and for patients without BAONJ - 19 months (from 4 to 84.7 months), and the risk of developing the condition determined from 1% 12 months after the start of treatment, to 11% by the fourth year [2]. According to other studies, the higher risk starts within 2 years of initiating BP therapy and increases four times after another 2 years [8], which correlates with the mean duration of BP therapy in the current study.

2. Risk factors associated with dental diseases and/or dental procedures

In our study, the most common dental procedures that patients underwent prior to their diagnosis or associated with the onset of symptoms of BAONJ are tooth extraction and denture placement. Barasch et al. also cited tooth extraction as a risk factor in their study [8]. Another study found that patients wearing dentures had a significantly shorter duration until the onset of BAONJ than patients who did not wear dentures. In addition, remission in prosthetic wearers is significantly slower [9]. In their study, Otto et al. comment on the development of the complication as a result of local infection or trauma to the bone or soft tissues. According to them, typical events that could precede BAONJ are significant periodontal inflammation, pressure wounds from dentures, other invasive procedures (tooth extraction) and other dentoalveolar surgical procedures, especially implant placement [10]. According to others, the risk of implant placement, endodontic treatment, and periodontal procedures is comparable to the risk associated with extraction [11]. In China, dental extraction (n = 24, 80%), periodontal disease (n = 5, 16.7%), poor oral hygiene (n = 8, 26.7%) and uncomfortable dentures were also identified as local factors in triggering BAONJ. (n = 3, 10%) [12].

Despite the above-mentioned facts, proving that invasive dental procedures undoubtedly hide a greater risk of developing BAONJ, about 25% of cases are spontaneous [6], which correlates with the data obtained in this study.

3. Other risk factors

Age and gender have been consistently reported as risk factors [3]. We, like Wang et al. [11], did not find a statistically significant difference between men and women who developed BAONJ, which differs from other studies in which the proportion of women is usually higher [13]. The higher incidence of this complication in the female population is likely a reflection of the underlying disease for which the agents were prescribed. Some authors point to a 9% increase in the risk of developing BAONJ with each passing decade [6].

Fig. 5. Last dental procedure before the onset of symptoms/diagnosing BAONJ

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraction</td>
<td>52.68%</td>
</tr>
<tr>
<td>Obturation</td>
<td>6.25%</td>
</tr>
<tr>
<td>Endodontic treatment</td>
<td>8.04%</td>
</tr>
<tr>
<td>Dentures</td>
<td>21.43%</td>
</tr>
<tr>
<td>Incision/other surgical manipulation</td>
<td>5.36%</td>
</tr>
<tr>
<td>Tartar removal</td>
<td>3.57%</td>
</tr>
<tr>
<td>Other</td>
<td>2.68%</td>
</tr>
</tbody>
</table>
The type of oncological disease has been reported as a risk factor. Multiple myeloma, breast, prostate, and lung cancers are most commonly mentioned. The data from this study correlates with those of other authors [4,14]. In addition, 9 of our patients were initially diagnosed with renal carcinoma, which correlates with other studies on the topic [7,15].

Tobacco and alcohol use has been cited as a risk factor for BAONJ [3,4,5,16]. Similarly to us, a case-control study also found that most patients with this diagnosis were smokers [8]. In China, 36.7% of patients were found to be smokers, and 30% of patients have poor drinking habits [12]. Another study found a relationship between smoking (p = 0.03) and BRONJ progression by χ² test [16]. Other authors report that concomitant use of BP and smoking may prolong the duration of complete remission [17]. Some concomitant diseases such as anemia [3,18], diabetes [6,18], systemic lupus, rheumatoid arthritis, etc. [3] have been cited as conditions that increase the risk of BAONJ. The high rate of anemia reported in our study correlates with a case-control study [8]. Nearly 1/4 of the patients in our study suffer from diabetes, which is similar to the results of a study in China, where 20% of patients with Osteonecrosis were diabetic [12]. According to other authors, diabetes does not necessarily lead to the onset of BAONJ and should not be considered an independent risk factor [19].

We did not identify patients with systemic lupus who developed BAONJ, and only two had rheumatoid arthritis. The most common concomitant diseases were hypertension and other cardiovascular diseases, while in China, only 16.7% of patients had high blood pressure [12]. The identified differences can be explained by social and other characteristics of the covered population in China, and the small number of patients in the sample.

The role of concomitant medication treatment is discussed in the literature. The immunosuppressive effects of chemotherapy have an adverse effect on the body and accordingly contribute to the onset of BAONJ [3,6]. Other authors, due to lack of case and control data, cannot conclude on the synergistic effect of chemotherapeutic agents in the onset of the condition [20].

Corticosteroids are associated with an increased risk of BAONJ [3,4,5,20]. This is due to impaired bone remodelling during treatment. Some specialists report that concomitant administration of corticosteroids with BP therapy may prolong the duration of complete remission of the BAONJ. In China, 13.3% of the subjects studied received corticosteroids or other immunosuppressive therapy [12].

Anti-angiogenic agents slow down the reparative processes in the oral cavity and are a predisposing factor for the development of BAONJ [3]. Denosumab is a human monoclonal IgG2 antibody that also inhibits angiogenesis [21]. In recent years, there have been a number of publications on its impact on the onset of the complication, especially in combination or with previous treatment with BP [21].

CONCLUSION

BAONJ is a complication associated with BP intake, which seriously impairs the quality of life of many patients. The investigation of identified in the literature risk factors with their occurrence in the studied population shows a correlation with the data of leading researchers. It is crucial to raise the awareness of dental practitioners, oncologists and patients regarding risk factors and prevention, and to encourage them to work together as a team to minimize the risk of developing this complication.

Abbreviations:
BP - Bisphosphonates -
BAONJ - Bisphosphonate-associated Osteonecrosis of the jaws
ZA - Zoledronic acid

Acknowledgements:
The paper was supported by the Ministry of Education and Science, The Republic of Bulgaria (National program “Young scientists and postdoctoral students”).

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J of IMAB. 2021 Jan-Mar;27(1)  https://www.journal-imab-bg.org  3547


DOI: https://doi.org/10.5272/jimab.2021271.3543

Received: 05/12/2019; Published online: 22/01/2021

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