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Risk factors influencing BRONJ staging in patients receiving intravenous bisphosphonates: a multivariate analysis

M. Nisi[1], F. La Ferla[1], D. Karapetsa[1], S. Gennai[1], M. Miccoli[2], A. Baggiani[2], F. Graziani[1], M. Gabriele[1]
[1]Department of Surgical and Medical Pathology, University of Pisa, Pisa, Italy; [2]Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

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Abstract. The objective of this study was to determine, retrospectively, the influence of various risk factors on the staging of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in a population attending a department of dentistry and oral surgery in Italy. Data were collected from the electronic and paper medical records of 90 patients receiving intravenous bisphosphonates. Two experienced and calibrated examiners used the American Association of Oral and Maxillofacial Surgeons updated 2009 classification to record the stage of BRONJ lesions. Multivariate ordinal logistic regression was performed to determine individual risk factors negatively affecting BRONJ staging. The factors associated with a worse BRONJ staging were high bisphosphonate cumulative dose (odds ratio (OR) 1.70, 95% confidence interval (CI) 1.02–2.82; $P = 0.04$), smoking (OR 1.80, 95% CI 1.03–2.80; $P = 0.04$), steroid intake (OR 1.70, 95% CI 1.00–2.87; $P = 0.05$), and a maxillary location of the lesion (OR 3.50, 95% CI 1.81–6.77; $P < 0.01$). Tooth extraction was the event that most negatively influenced BRONJ staging (OR 1.60, 95% CI 1.00–2.81; $P = 0.05$), in comparison to other events such as prosthetic trauma, implant treatment, oro-dental infection, and periodontal disease. Certain clinical and medical risk factors may determine a more severe staging of BRONJ lesions. Future studies are necessary to confirm these findings.

Keywords: BRONJ; staging; risk factors; multivariate analysis.

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Bisphosphonates (BPs) are unstable equivalents of pyrophosphate that bind selectively to bone and are supposed to act selectively on osteoclasts during high bone turnover, resulting in an anti-resorptive effect.[1] BPs are indicated in the treatment of bone metastases, especially in breast and prostate cancers, as well as in multiple myeloma, osteoporosis, and malignant hypercalcaemia, where these agents produce a significant reduction in skeletal complications, such as pathological fractures and spinal cord compression.

Despite the high efficacy of BPs in the treatment of several diseases, some side effects have been reported, including osteonecrosis of the jaws.[2,3] In 2003, Marx

Table 1. Summary of pre-operative clinical variables.

Preoperative clinical variables	Stage 1, *n* (%)	Stage 2, *n* (%)	Stage 3, *n* (%)
Age, years[a]	67.0 ± 12.4	69.0 ± 8.3	69.0 ± 11.5
Gender, male	6 (35%)	19 (38%)	8 (35%)
Smoking	5 (29%)	13 (25%)	9 (38%)
Heart disease	1 (6%)	3 (6%)	2 (8%)
Hypertension	4 (24%)	10 (20%)	5 (22%)
Liver disease	1 (6%)	2 (4%)	2 (8%)
Diabetes	2 (12%)	4 (8%)	3 (13%)
Other disease	5 (29%)	10 (20%)	3 (13%)
Radiotherapy	13 (76%)	35 (70%)	20 (87%)
Chemotherapy	16 (94%)	47 (94%)	23 (100%)
Steroids	11 (65%)	29 (57%)	10 (43%)
BP cumulative dose, mg[a]	67.0 ± 22.7	71.0 ± 25.1	76.0 ± 16.5
Location, mandible	14 (82%)	33 (66%)	11 (65%)
Tooth extraction	11 (65%)	27 (54%)	17 (70%)
Implantology	2 (12%)	0	0
Prosthesis	0	8 (16%)	1 (4%)

BP, bisphosphonate.

[a] The values reported for the variables 'age' and 'BP cumulative dose' are expressed as the mean ± standard deviation.

reported the first cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ), and since then, many other cases have been reported.[3–5] BRONJ has been clearly defined as a clinical scenario characterized by three diagnostic features: (1) current or previous treatment with a BP; (2) the presence, for longer than 8 weeks, of exposed bone in the maxillofacial region; and (3) no history of radiation therapy to the jaws.[6] Moreover, recent evidence has suggested that a non-exposed form of BRONJ may represent an insidious clinical variant that clinicians should always consider in their diagnostic process.[7,8]

The aetiology of BRONJ remains unknown. The multifactorial pathogenesis is related to many local and/or general factors, including disruption of the normal bone turnover cycle,[9] compromised angiogenesis,[10] inhibition of oral cell wound healing,[11] genetic polymorphisms,[12,13] and microbial biofilm.

Several recent studies have focused on the risk factors for developing BRONJ. In the recent position paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS), BRONJ risk factors are categorized as drug-related, local, demographic and systemic, or genetic.[6] Obesity and smoking were recently associated with BRONJ, but the same study showed that the most relevant risk factor was zoledronate use.[14]

Therefore, the purpose of the present study was to collect and analyze the data from 90 patients attending the Department of Dentistry and Oral Surgery of the University Hospital of Pisa, Italy, and presenting with stage 1, 2, or 3 BRONJ lesions, in order to determine the influence of various risk factors on BRONJ staging.

Materials and methods

Study design and sample

To address the research hypothesis, the investigators designed a retrospective study involving 90 patients. Written consent for data processing and the publication of clinical photographs was obtained from all subjects at the time of the first visit.

The study included subjects affected with BRONJ, referred and treated in the department of dentistry and oral surgery of the study hospital in Pisa from January 2004 to December 2012. The study inclusion criteria were based on the AAOMS 2009 position paper,[6] and comprised a history of BP therapy and the presence of intraoral lesions (e.g., exposed necrotic bone, pus, exudates, fistulas) or extraoral manifestations of swelling or fistulae persisting longer than 8 weeks. The diagnosis of BRONJ was made by two calibrated and experienced examiners (MN, FLF) on the basis of both a clinical and a radiographic examination (orthopantomography); in the case of doubt, an expert operator was consulted (MG). All patients were scheduled for surgical treatment within 4 weeks of the BRONJ diagnosis. Patients were seen for control visits at 1 week, 1 month, 3 months, and 6 months after surgery.

Study variables and data collection

BRONJ staging, the primary outcome, was defined according to the AAOMS updated 2009 classification.[6] Data sources were the subjects' electronic and paper medical records. Data collection was performed by a single examiner (MN) and was centred on the demographic and medical variables reported in Table 1. As all patients were on intravenous BP treatment, information on the dose, number of infusions, and number of months from initial to most recent infusion were also collected. Medication use was recorded as a binary outcome for cancer chemotherapy, anti-angiogenic drugs, and steroid use. Comorbidities were recorded as a binary outcome based on a positive clinical diagnosis.

Statistical analyses

Data were collected in a spreadsheet (Excel 2013; Microsoft, Redmond, WA, USA) and proof-read for entry errors. The database was subsequently locked, imported into SPSS v.17.0 for Windows (SPSS, Inc., Chicago, IL, USA) and R v.2.10 (Statistics Department of the University of Auckland, Auckland, New Zealand), formatted, and analyzed. Greek letters were assigned to the variables so that the statistician was blinded to what they were. Multivariate ordinal logistic regression was performed to determine the influence of risk factors on BRONJ staging.

Results

Sample characteristics

Ninety subjects were identified and included in the present study; 57 were female (63%) and 33 were male (37%), and their mean ± standard deviation age was 66.3 ± 10.5 years. Characteristics of the population included are reported in Table 1. All subjects were on intravenous