Disease Stage and Mode of Therapy Are Important Determinants of Treatment Outcomes for Medication-Related Osteonecrosis of the Jaw

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Purpose: The treatment of patients with medication-related osteonecrosis of the jaw (MRONJ) is challenging. The purpose of the present study was to estimate the frequency and identify the factors associated with clinical improvement during treatment.

Patients and Methods: We designed and implemented a retrospective cohort study and enrolled a sample of subjects diagnosed with MRONJ between 2004 and 2015. The primary predictor variables were a set of heterogeneous variables grouped into the following categories: demographic (age and gender) and clinical (location of necrosis, therapy duration, medication type, disease stage, and treatment type). The primary outcome variable was the treatment outcome, defined as stable or worse and improved or healed. The descriptive, bivariate, and multiple logistic statistics were computed, and statistical significance was defined as $P < .05$.

Results: The sample included 337 subjects with a mean age of 68.9 years. Of the 337 subjects, 256 were women (76%). A total of 143 patients (42.2%) experienced spontaneous necrosis. Twenty-four (7.1%) had had exposure to targeted antiangiogenic agents. Those with stage 1 or 2 disease were more likely to have better outcomes than those with stage 3 disease (stage 1, adjusted odds ratio [OR] 3.4, $P = .005$; stage 2, adjusted OR 2.2, $P = .03$). Treatment type was a significant variable. Subjects undergoing surgery were 28 times more likely to have a positive outcome than those receiving nonoperative therapy (adjusted OR 28.7, $P < .0001$).

Conclusions: Subjects with MRONJ who presented with less severe disease or who underwent operative treatment were most likely to have improvement or complete healing of their MRONJ-related lesions.

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Osteonecrosis of the jaw (ONJ) related to antiresorptive medications has received considerable attention in the scientific and lay communities since it was first described more than 10 years ago. The relationship between antiresorptive therapy and ONJ was established in 2001, following an influx of patients to our facility with exposed, necrotic bone isolated to the jaws. These patients were mostly cancer patients who had received chemotherapeutic regimens that varied widely in accordance to the tumor type and characteristics. The only evidence that linked these cases was a history of antiresorptive therapy. The occurrence of necrotic bone in osteoporotic patients receiving oral antiresorptive therapy with no history of cancer or chemotherapy formed a convincing association between jaw necrosis and antiresorptive therapy. In 2004, our institution published the first peer-reviewed report characterizing the clinical

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presentation, suspected pathophysiology, and associated risk factors within a cohort of patients who had been exposed to bisphosphonates.[1] At that time, a relational database (Microsoft Access) was designed to capture various aspects of this disease process, including clinical, epidemiologic, and treatment outcomes data. As new parameters of ONJ presentation and treatment emerged during the previous 10 years (ie, medications, treatment strategies), new data points were appended to the database.

The purposes of the present study were to *1)* describe the characteristics of a sample of patients with medication-related ONJ (MRONJ), *2)* identify the factors associated with the development of MRONJ, and *3)* identify the variables associated with favorable outcomes. We hypothesized that one or more variables would be associated with favorable outcomes for patients with MRONJ. Our specific aims were to *1)* summarize the descriptive statistics of the sample and *2)* examine the factors associated with the outcome (healed or improved vs stable or worse) after treatment of MRONJ.

Patients and Methods

STUDY DESIGN AND SAMPLE

We designed and implemented a retrospective cohort study and enrolled a sample derived from the population of subjects with a diagnosis of MRONJ who had received treatment between 2004 and 2015. The sample inclusion criteria were a diagnosis of MRONJ according to the clinical and radiographic findings (Table 1) and a follow-up duration of at least 6 months. The exclusion criteria for this sample were exposure to radiation therapy focused on the head and neck region, medication dosage or duration that could not be verified, malignant disease that directly involved the jaws, and an insufficient follow-up duration. This study met the criteria for exemption by the institutional review board.

STUDY VARIABLES

Predictor Variables

The predictor study variables included a heterogeneous group of variables segregated into the following categories: *1)* demographic, *2)* clinical data, and *3)* treatment modality. The demographic variables included gender and age at MRONJ diagnosis, the indication for antiresorptive or antiangiogenic therapy (malignant or nonmalignant disease), the medication used (bisphosphonate, receptor activator of nuclear factor kappa-B ligand inhibitor, or antiangiogenic agent), duration of exposure, steroid therapy, anatomic location of the exposed bone (maxilla or mandible, or both), and the disease stage at presentation. The disease stage was determined using the American Association of Oral and Maxillofacial Surgeons (AAOMS) staging criteria (Table 1).[2] The treatment types were surgery (alveolectomy or marginal or segmental resection) and nonoperative therapy (systemic antibiotics, antimicrobial rinses). The subjects were followed up continuously until the endpoint of death, the establishment of healed bone, or loss to follow-up.

Table 1. AAOMS STAGING FOR MRONJ

Stage	Description
0	No clinical evidence of necrotic bone, but nonspecific clinical findings, radiographic changes, and symptoms present
1	Exposed and necrotic bone or a fistula that probes to bone in asymptomatic patients with no evidence of infection
2	Exposed and necrotic bone or a fistula that probes to bone, associated with infection, evidenced by pain and erythema in region of exposed bone with or without purulent drainage
3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and ≥1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (ie, inferior border and ramus in mandible, maxillary sinus, and zygoma in the maxilla), resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of the sinus floor

Abbreviations: AAOMS, American Association of Oral and Maxillofacial Surgeons; MRONJ, medication-related osteonecrosis of the jaw.

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Outcome Variable

The treatment outcome was the primary outcome variable and was grouped as stable or worse and improved or healed. The patients were considered healed if complete mucosalization of the exposed bone had occurred with pain relief. The patients were considered improved if they were symptomatically better or had moved to a lower disease stage after treatment. The subjects were considered stable if their disease had not advanced to a higher stage. For patients with stage 1 disease, this was considered a positive outcome, because patients with stage 1 disease are, by definition, asymptomatic. The patients' status was considered worse if they demonstrated progressive pain, infection, or persistent bone exposure after treatment, with advancement to a higher stage.