Ostenecrosis of Jaw (ONJ) Related to Bisphosphonates and other Drugs: Prevention, Diagnosis, Drug Surveillance, Treatment. Update 2014 Alessandria, Sabato 10 Maggio 2014

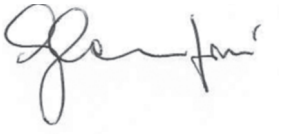
Cari lettori, amici e colleghi,
sono particolarmente onorata dall'invito a presentare i proceedings del Convegno Nazionale su Osteonecrosi delle Ossa Mascellari (ONJ) da bifosfonati e altri farmaci, dedicato quest'anno a "Prevenzione, diagnosi, farmacovigilanza, trattamento-update 2014".
In verità, il titolo del Convegno già chiarisce l'innovativa visione che ha guidato la strutturazione dell'evento per il 2014. Infatti, in questi ultimi anni ci si è dovuti occupare non solo di bifosfonati, ma anche di altre classi di farmaci accomunate da simile reazione avversa alle ossa mascellari. Finalmente, si comincia nella comunità medica e odontoiatrica italiana, invitata a partecipare all'evento, a condividere *good practice*, grazie a una costante attività di studio, ricerca clinica e divulgazione di una visione unitaria della malattia e della sua prevenzione I, II e III.
In questo nuovo scenario, numerosi clinici e ricercatori italiani hanno risposto all'invito e inviato oltre 70 abstract, nelle diverse categorie scientifiche del Convegno (i.e. casistiche di ONJ, case reports, prevenzione/follow-up, trattamento ONJ); questi, revisionati, saranno pubblicati nel presente special issue. Infatti, in collaborazione con la SIPMO (Soc. Italiana di Patologia e Medicina Orale), la Segreteria Scientifica ha deciso di allestire, grazie a un efficiente e puntuale editorial board, un volume consultabile online, *open-access* e indicizzato su PubMed.

Mi piace ricordare che il primo Gruppo Italiano di lavoro sull'Osteonecrosi dei Mascellari è stato proprio quello della Rete Oncologica del Piemonte e della Valle d'Aosta: esso si costituì nel novembre 2005 durante un workshop tenutosi ad Alessandria, organizzato da Vittorio Fusco, Guido Bottero e collaboratori, motivati dall'insorgenza dei primi casi di osteonecrosi delle ossa mascellari e mandibolare in pazienti trattati con bifosfonati. Nel giro di pochi anni, siamo stati tutti coinvolti e spinti a collaborare e comunicare per la necessità e volontà di risolvere e prevenire questa malattia. Nascono così le casistiche retrospettive multicentriche, le prime *letter to Editor* per presentare alla comunità internazionale la nostra timida opinione sulla malattia, fino all'idea, sbocciata proprio ad Alessandria nel 2011, di stilare in lingua italiana delle raccomandazioni per la prevenzione e cura della ONJ, sulla base di quanto conosciuto. Le stesse che grazie alla collaborazione di molti di noi sono adesso open access su www.sipmo.it e sono incluse - con riferimento ai loro principi e alle indicazioni per i pazienti oncologici - nelle Raccomandazioni del Ministero della Salute per la promozione della salute orale nei pazienti adulti con patologia neoplastica (dal 1 aprile 2014).
È questa l'occasione che aspettavo, a nome degli esperti di medicina orale e degli odontoiatri italiani, per ringraziare l'amico Vittorio Fusco e il Gruppo di lavoro Osteonecrosi dei Mascellari della Rete Oncologica del Piemonte e della Valle d'Aosta, per averci permesso di dialogare e confrontarci, per aver creato, primi tra tutti, questa importante piattaforma di scambio e di crescita.
Infine, un autentico e caloroso ringraziamento al Comitato di Revisori che ha lavorato sollecitamente nei mesi precedenti la pubblicazione dei *proceedings* e alla Segreteria Tecnica della SIPMO per il costante supporto fornito.

Con l'augurio di un proficuo convegno e di una interessante lettura dei lavori scientifici presentati, saluto tutti coloro che hanno creduto e continuano a credere che l'unione fra le discipline fa la forza e permette di offrire ai nostri pazienti una vita migliore.

Palermo, 27/04/2014

Giuseppina Campisi
Past-President SIPMO



Contents

Category 1

Osteonecrosis of the jaw (ONJ) as a possible adverse side effects of bisphosphonate therapy in fibrous dysplasia and McCune-Albright syndrome

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Background. McCune-Albright syndrome (MAS) is a rare multisystem disorder characterized by the triad of polyostotic fibrous dysplasia (FD), endocrine disorders, and café-au-lait skin pigmentation1. Ninety percent of MAS patients have FD lesions in the craniofacial area, resulting in significant orofacial deformity, malocclusion, dental disorders, bone pain, and compromised oral health. Osteonecrosis of the jaw (ONJ) has recently been described as an adverse side effect of bisphosphonate therapy and is often correlated to infections or injury of the oral cavity2.
Aim. The aim of the study is to investigate evidence of clinical and/or radiological signs of ONJ in FD/MAS pediatric patients due to bisphosphonate therapy.
Study design. 13 FD/MAS patients (6 males and 7 females, aged 7 to 27 years, mean age 20 years and 4 months) were enrolled in the study. All patients during pediatric age have been treated with 1mg/kg/day pamidronate infusion for three days at 4-6 months intervals for an overall period of 30 months. All patients underwent medical investigation and complete extra-oral and intra-oral clinical examination to detect soft tissues swelling, dental caries, tooth mobility, malocclusion, bone exposure and/or fistulas. Ortopantomography, CT and/or MR imaging were evaluated in all cases.
Results. No patient developed ONJ. Dental eruption was normal in all cases and only three patients were treated for dental caries. None of them showed tooth mobility, bone exposure or fistulas or radiological signs different from jaw FD such as radiolucent cystic areas with a thin cortex (Fig. 1). The major phenotypic expression of MAS was malocclusion (4 patients).
Conclusion. In spite of the low number of patients enrolled, results confirm that, in this population, ONJ can be ruled out as a chronic adverse side effect of bisphosphonate therapy. Good oral hygiene, careful dental care and follow-up are highly recommended in these patients.

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Category Chosen
Descrizione di Casistiche di ONJ

Computed Tomography (CT) follow-up evaluation of patients undergoing surgery for Osteonecrosis of Jaw (ONJ)

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Background. Computed Tomography (CT scan) has a possible role of follow-up evaluation of jawbone sites after surgical treatment of Osteonecrosis of Jaw (ONJ) due to Bisphosphonate Treatment (BRONJ). There is no uniform literature data about the concept of “bone healing” after surgery.

Patients and methods. Eleven patients affected by BRONJ and submitted to osteonecrotic lesion removal have been recalled in order to check evolution of healing sites with CT scan. Out of 11 patients, 8 were under zoledronic acid treatment and 3 under oral alendronate. ONJ sites: 3 maxillary, 7 mandibular, and 1 both.
All the patients had been submitted to surgery with Piezoelectric technique. All 11 patients appeared to be clinically healed (no areas of bone exposure and no symptoms or signs of ONJ).
Results. In the wound areas, mandibular TC scans showed increase of medullary sclerosis and of bone density, according to Hounsfield measurements (in comparison with the correspondent contralateral healthy area), in all bone sites, out of total 8 examined mandibular sites.
These signs could not be showed on maxilla areas due to apparent lack of reactivity of bone tissue (the level of bone density of sectors next to the resection site was comparable to the healthy ones, placed in contralateral area).
Conclusions. CT scans of larger series of BRONJ patients are needed to draw conclusions; however different evaluations in mandibular and maxillary sites are recommendable.

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Category Chosen 1

Antiangiogenic agents and target therapy effect on ONJ occurrence: a pharmacovigilance monoinstitutional report

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Background. Osteonecrosis of Jaw (ONJ) has been reported since 2003 in patients receiving Bisphosphonates (BPs) as treatment of metastatic bone lesions of solid tumours, myeloma and osteoporosis. Since 2005 in our hospital an institutional ONJ multidisciplinary team was created. In recent literature, reports were published about possible role of angiogenic drugs, used in several tumor diseases as able to block the activity of angiogenesis and thus reduce tumor growth. On 2010, alert was released by EMA (European Medicine Agency) about bevacizumab (Avastin®, approved in Europe on 2005) and sunitinib (Sutent®, approved on 2006).
Materials and methods. We reviewed charts of all patients with diagnosis of ONJ after BP and/or antiangiogenic agent therapy observed between August 2005 and February 2014 at our centre, both from our hospital Oncology-Hematology Department (502 pts receiving BPs; 80 receiving bevacizumab; 17 receiving sunitinib) and referred by other specialists.
Results. We registered 46 ONJ cases, all reported to Italian Drug Safety Surveillance Safety System (AIFA) . Out of 46, 23 were patients from our hospital Oncology-Hematology Department and 23 were referred to our ONJ team by other hospitals or by dentists. They were: 19 men (41%) and 27 women (59%). Median age 66 years (range 46-86). Disease: breast cancer in 19, prostate cancer in 8, myeloma in 9, other tumor type in 4, osteoporosis in 6. We observed 4 cases of ONJ in patients receiving antiangiogenic agents: 1 case after bevacizumab alone; 3 after sunitinib and BPs.
Conclusions. It is necessary to apply careful attention to patient oral health when antiangiogenic drugs are administered (with or without BPs) .
If patients undergoing antiangiogenic treatment (bevacizumab, sunitinib, etc.) without BPs should undergo proper preventive dentistry measures before starting treatment (as well as it is recommended for patients receiving BPs) should be object of research.

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Category Chosen 1

The “C.R.O.MA.” project: a care pathway for bronj prevention

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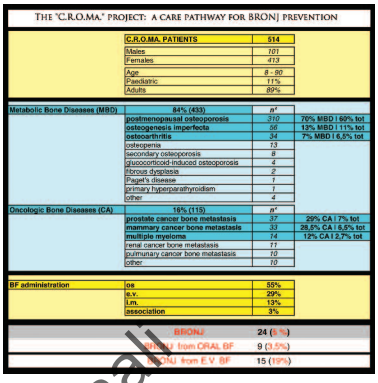

Objectives. To portray the “C.R.O.MA.” project (Coordination of Research on Osteonecrosis of the Jaws) of "Sapienza" University of Rome, to perform a descriptive study on the 7 years activity data and to create a dedicated online database (DB).
Materials and methods. To minimize risks by optimizing care, in 2007, in our Department of Oral and Maxillofacial Sciences we created a care pathway for patients on previous, current or planned therapy with bisphosphonates (BF), first by collecting their data in a dedicated online DB and then following three main paths: A) prevention, B) conservative/periodontology, C) surgery.
Results. From January 2007 to March 2014, 514 adult (89%) and paediatric (11%) patients were examined and recorded on the DB. 101 patients were males, 413 females, aged 8-90 years. 441 were affected by metabolic bone diseases (MBD) and 115 by cancer (CA), 42 patients in co-morbidities. For the OM group the most represented were the post-menopausal osteoporosis (70% MBD I 60% tot.), osteogenesis imperfecta (13% MBD I 11% tot) and osteoarthritis (7% MBD I 6.5% tot). For the CA group, the main types were prostate cancer (29% CA I 7% tot), breast cancer (28.5% CA I 6.5% tot) and multiple myeloma (12% CA I 2,7% tot). Overall, 7% were also taking glucocorticoids, while still a very small ratio of patients were under anti-neoangiogenic drugs therapy (4 cases). Overall, 24 cataloged patients with BF related osteonecrosis of the jaws were found among 514 subjects: 15 of the total 80 (19%) who have been treated by i.v. administration (zoledronic acid) and 9 out of 250 total (3.5%) under oral BF therapy.
Conclusions. The risk of BRONJ is still low, particularly for the oral administered therapies. Nevertheless, if applied to everyday clinical practice, international evidence based prevention protocols are of paramount importance and can reach lower and lower percentage of adverse events from BF therapy, aided also by the networking using the online database.

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Category Chosen 1

ONJ (osteonecrosis of jaw) in myeloma patients: a monoistitutional experience of 117 patients treated with bisphosphonates

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Background. Bisphosphonates (BPs) are strong osteoclast inhibitors, used for osteoporosis, bone pain, hypercalcaemia in myeloma patients. Osteonecrosis of the Jaw (ONJ) is a complication well described in patients treated with IV BPs, such as Pamidronate and Zoledronic Acid. The percentage of patients with multiple myeloma treated with BPs and developing ONJ was 6-26% in first literature series. We investigated whether the occurrence of ONJ decreased after implementation of preventive measures in patients who received BPs, in a single center experience.
Patients and Methods. We reviewed all 117 patients with Multiple Myeloma treated with BPs between 2005 and 2013. They were observed by a multidisciplinary team (including maxillofacial surgeons, dentists, hematologists, oncologists, nurses, radiologists, nuclear medicine and infective disease specialists) and underwent a baseline mouth assessment (dental visit, orthopantomogram, eventual tooth avulsion or dental care). Patients were classified in 3 groups : a) "historic group" (21 patients starting BP treatment before 2005) b) "screening group" (20 patients starting BPs without preventive measures, since 2005) c) "prevention group" (76 pts who started therapy after preventive visit).
Results. One hundred and seventeen patients were included in this analysis. ONJ was observed in 3/21 patients (14.2%) in group a, in 2/20 patients (10%) in group b, and in no patient from group c (0/76).
Conclusions. Our data confirmed an important reduction of ONJ in multiple myeloma patients treated with BPs, if preventive measures are applied. Implementation of prevention and reduction of cumulative doses of BPs could have contributed to decreasing incidence of ONJ. A longer follow up is necessary to confirm positive results herein reported.

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Category Chosen 1

A pilot study on the association between bisphosphonate concentration in sequestered bone and osteonecrosis of the jaw

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Background. The rationale of our investigation is related to bisphosphonates (BP) ability to bind bone tissue, which, in turn, strongly affects drug efficacy and adverse effects, in particular the osteonecrosis of the jaw (ONJ) (1). A putative association between drug concentrations, in bone sequestrations of these patients, and ONJ development can be supposed (2).
Aim. The aim of this study is to detect and quantify BPs in sequestered bone, spontaneously or surgically removed from patients with ONJ.
Methods. Among patients referring to Unità di Odontostomatologia II of the A.O. Universitaria "San Paolo" of Milan, those subjects with BP-related ONJ and who underwent to spontaneous or surgical removal of bone sequestration, were recruited. Drug dosage was conducted by means of high- performance liquid chromatrography technique coupled to mass spectrometry.
Results and conclusions. We analyzed sequestered bone specimens obtained from 27 patients with ONJ related to alendronic acid and/or zolendronic acid therapies. ONJ. The concentration of BP in bone sequestration was low or resulted not detectable. Our findings arise the need of further studies to elucidate the putative association BP concentration-ONJ development as well as a better comprehension of ONJ pathogenesis.

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Activity of the bisphophonate related oral pathology service of the S. Luigi Gonzaga Hospital

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Objective. The objectives of the "Bisphosphonate related oral pathology Service" are 1) to evaluate the oral condition of the oncologic patients before the beginning of the therapy with bisphosphonate in order to reduce as less as possible the oral risk factors, 2) to follow up the patients during all the period of treatment in order to intercept as soon as possible the onset of the disease and 3) to treat the patients affected from bisphosphonate related osteonecrosis of the jaw (BRONJ). We wanted to compare our population of patients taking bisphosphonates and our results with literature data.
Methods. On PubMed were searched different works about prevalence of BRONJ, of localization, of oral risk factors and of resolution after surgery. The data of literature were compared with our population.
Results. From may 2011 until December 2013, 91 patients (48 males, 43 females) taking bisphosphonates were visited in our Service. BRONJ occurred in 23% of this population, 16,6% were oncologic patients. Prevalence of BRONJ described in literature varies from 1,2% to 28%, although in a study with follow-up it is attested to 13.3%. 60% of the BRONJ was localized in the mandible, 35% in the maxilla, and 5% in both mandible and maxilla. 57% of the BRONJ occurred after extractive procedures, 38% were considered spontaneous and only 5% occurred on a site of periodontal disease.
In a work conducted by a group of researchers from Turin, triggering causes for BRONJ were so divided: 59,5% from extractive procedures, 27% spontaneous and 13,3 from periodontal disease.
Surgical treatment was necessary for 16 patients, but on 2 patients (12%) BRONJ recidivated in less than 6 months.
Conclusions. The percentages about prevalence of BRONJ, of localization, of oral risk factors and of resolution after surgery in our population is similar to the data reported in literature.

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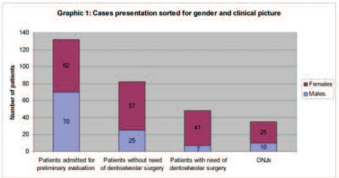
Clinical experience of the IRCCS San Martino, IST of Genova with bisphosphonate-related osteonecrosis of the jaw



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Introduction. This work to report data and clinical experience over a six-year period of the Unit Odontostomatology and Maxillofacial Surgery of the IRCCS San Martino – IST of Genova regarding to the bisphosphonate-related osteonecrosis of the jaw (BRONJ). From June 2008 the "Service of prevention for patients suffering from systemic diseases" works preventing, monitoring and treating side effects of bisphosphonates (BF) on jaw bones.
Methods. Patients admitted to the clinic received detailed investigation of their medical history, especially regarding BF administration. A detailed clinical examination was then carried out. All patients were added to scheduled follow-up and clinical findings were registered in the medical record.
Results. 297 patients were admitted to the clinic. Patients preliminary evaluated before intravenous (IV) BF administration for metastatic neoplasm were 132 (44,4%). Other 130 patients (43,8%) were already under BF treatment at presentation. Patients presenting with ONJ were 35 (11,8%); 5 had received oral BF for osteoporosis for more than 3 years. All patients with ONJ were treated conservatively without recurrence at follow-up.
Comparing data with a previous report, the average number of patients admitted for preliminary evaluation before IV BF administration augmented from 4,2 per year in the first two-year period, to 32,3 per year in the sequent four-year period. While the average number of ONJs decreased from 12,0 per year in the first period, to 3,1 per year in the sequent period.
Conclusion. Systematic preliminary evaluation of patients and scheduled follow-up represent the best way to prevent ONJ. Data exposed prove an increase in the preventive activity of the Service; decreasing of ONJs may indicate an important success achieved by its preventive activity. When a patient presents with early stage BRONJ, conservative therapy avoiding any aggressive surgery is the best choice for treatment, reaching in most cases satisfactory results.

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Category Chosen 1

ONJ (osteonecrosis of jaw) epidemiology on years 2003-2013. Increase and decrease of ONJ occurrence: possible reasons and pitfalls

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After first reports of ONJ cases in patients(pts) treated with Bisphosphonates (BP) in years 2003-2004, an explosion of case series and case reports were published wordwide. We hypothesized the possible reasons of this timing, with ONJ incident cases apparently increasing in 2004-2007 years: a) increased prescriptions of more potent BPs in cancer pts since '90s; b) higher ONJ risk due to zoledronic acid, and after shorter median treatment duration (compared with pamidronate); c) unrare shift from pamidronate to zoledronate treatment (2001-2004); d) increased ONJ awareness, and post-hoc diagnosis (both in cancer and osteoporotic pts) of "prevalent" cases (diagnosed in 2003-2005 years but actually suffering from months/years of a misdiagnosed ONJ). Prevention (risk reduction) measures were recommended on the base of expert opinions and some studies confirmed their probable value, so that a reduction of ONJ frequency was expected in the following years. Actually, no recent literature data are available with few exceptions (1-3).
On 2008-2013 years, contradictory phenomena could have influenced the ONJ incidence (increased/decreased) in drug-exposed population at risk for ONJ: i) efficacy of prevention measures; ii) reduction of BP prescriptions and/or BP treatment duration in myeloma and bone metastatic cancer pts (new guidelines); iii) reduction of (false new) "prevalent" cases; iv) possible increase of off-label or borderline BP prescriptions (cancer pts without bone metastases; CTIBL treatment after endocrine therapy; asymptomatic bone metastases in castration-sensitive prostate cancer pts); v) large use of antiangiogenic agents (i.e., in Renal Cell Cancer pts); vi) increasing prescriptions of deno-

sumab (and possible shift from zoledronate to denosumab); vii) increasing awareness of limits of purely clinical AAOMS definition of ONJ (exposed bone) and of possibility of "unexposed" ONJ cases.
Population studies and ONJ registry data collections are urgently needed.

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Category Chosen 1

Is bone scan (Tc99 scintigraphy) uptake predictive of clinical onset of osteonecrosis of jaw (ONJ)?

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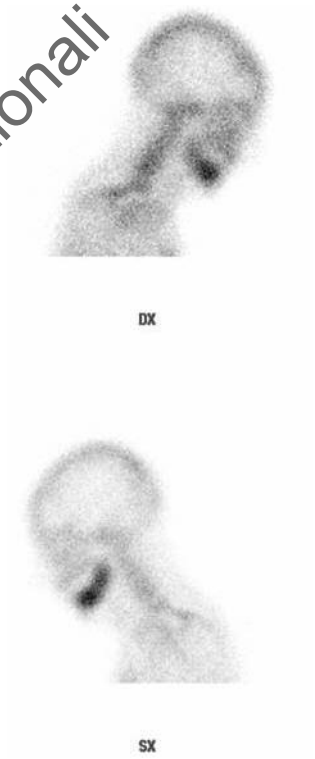

Background. Data about early detection of ONJ by Bone Scan (99mTc-MDP scintigraphy)(BS) have been occasionally published. (1,2). Following data are in favour: a) BS is an imaging technique with high sensitivity; b) sporadic cases of early jawbone (maxilla or mandible) uptake have been reported, occasionally even months or years before clinical evidence of ONJ (bone exposure); c) the BS is performed periodically in patients with skeletal metastases to check out the status of disease activity and the response to specific treatments; consequently the research for early ONJ does not involve additional costs. Potential limitations include: a) maxilla or mandibular uptake could be due to metastatic lesions; b) BS is a technique with low specificity: beside neoplastic one, bone traumatic, inflammatory, degenerative lesions can determine an uptake; c) an undefined proportion of patients (even without any active tumor disease) shows jaw uptakes, due to dental diseases widely seen in the general population (abscesses, denture ulcers, periodontal disease, etc.); c) even in BP-related ONJ suspected cases, jaw uptake may be due to infections that are not necessarily connected to the osteomyelitis component of ONJ.

Methods. We retrospectively conducted a study of routine BS performed in 12 ONJ patients treated with BPs (8 with breast cancer, 4 prostate cancer); BS was performed 6-12 months prior to definitive ONJ diagnosis. Two Nuclear Medicine specialists reviewed images.

Results. 6-12 months prior to diagnosis, 8/12 BS were positive (evident jaw uptakes in ONJ sites), 3/12 were doubtful (moderate uptake) and 1 negative.

Conclusions. These preliminary data are interesting and challenging. A case-control study has been designed with different patient groups, including: ONJ cases; patients treated with BP and not suffering from ONJ; cancer patients not receiving BPs.

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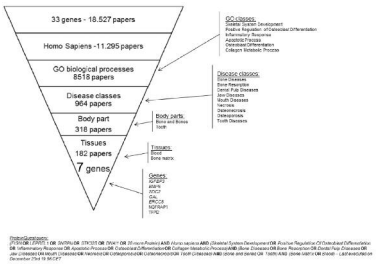
Effects of bisphosphonate treatment on DNA methylation inosteonecrosis of the jaw



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Aim. DNA methylation has a key role in gene regulation in many tissues, but little is known of its involvement in bone homeostasis. No information is available about bisphosphonates related osteonecrosis of the jaw (BRONJ) and altered methylation.
This study investigates the role of DNA methylation in the pathogenesis of BRONJ as a consequence of treatment with intravenous nitrogenous-containing bisphosphonates (zoledronic acid).
Methods. We performed an epigenome-wide association study using the Illumina Infinium Human Methylation27 BeadChip assay in peripheral blood samples from 80 patients treated with nitrogenous BP, including 40 who developed BRONJ.
Results. Logistic regression analysis confirmed a positive association between cumulative exposure and risk of developing BRONJ. The analysis of the cumulative BP-exposure distribution indicated that cases were slightly more exposed to BP than controls, and that cases diagnosed with BRONJ in both mandible and maxilla were significantly more exposed to BP than controls. Logistic regression analysis confirmed the positive association between cumulative BP exposure and risk of BRONJ. 34 probes, corresponding to 33 differentially methylated (DM) genes, were significantly associated with cumulative BP exposure; ERCC8, LEPREL1, and SDC2 genes showed highly statistically significant differences in methylation levels by BP exposure.
Conclusion. Enrichment analysis, combining DM genes with genes involved in HMG-CoA reductase pathway, evidenced that BP treatment can affect the methylation pattern of genes involved in extracellular matrix organization, and inflammatory response, leading to more frequent adverse effects such as BRONJ. Differences in DNA methylation induced by BP treatment could be involved in the pathogenesis of bone lesions. Disturbing the healing at any stage, particularly the formation of the provisional matrix, could compromise the entire process and lead to a more frequent occurrence of side effects such as BRONJ.

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Surgical approach in the bisphosponate-associated osteonecrosis of the jaws: a retrospective case series

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Aim. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) may be treated conservatively or by surgery. The purpose of the current retrospective chart review is to describe the outcomes of surgical approach in the management of B-ONJ.

Methods. The clinical charts of 10 patients affected by BRONJ in 11 sites were identified. The patients (8 females, 2 males; mean age 69.5 ± 9.33) were consecutively treated with surgical approach at the Oral Surgery Unit of "Sapienza" University of Rome from November 2008 to December 2013. The surgical protocol included antibiotic (amoxiclavulanate) administration 15 days before and 15 days after surgery; mouth disinfection with perioperative chlorhexidine gluconate 0,20%; general or local anaesthesia with mepivacaine 3% without epinephrine; sequestrectomy and surgical debridement with piezo surgery®; platelet-rich plasma application and 4-0 VICRYL suture.
Results. Five patients were affected by metabolic bone diseases (osteoporosis, Paget's disease) and the mean exposure to oral bisphosphonates (BP) was 67±45.68 months. Five patients suffered from metastatic cancer (breast cancer, prostate cancer, multiple myeloma) and the mean exposure to i.v. zoledronic acid was 19.8±10.54 months. Five lesions were located in maxilla (45.46%) and six in mandible (54.54). In five cases the onset of BRONJ was spontaneous (45%); in the other cases the BRONJ was probably trigged after dental extraction (28%), or due to a prosthetic decubitus (18%) and in one cases after implant placement (9%). At a mean follow-up of 23±11.34 months, 100% of patients appeared clinically healed with closure of mucosal dehiscence and absence of any clinical sign or symptom as well as radiographic pathological feature.
Conclusion. Within the limitations of the current chart review, the results showed that surgical approach can provide favorable outcomes in the treatment of B-ONJ.

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CATEGORY 1

Bisphosphonate-Related osteonecrosis of the jaws in patients affected by osteometabolic diseases: a serial case analysis

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Introduction. The bisphosphonates are the most commonly prescribed antiresorptive drugs for the treatment of metabolic disorders. However, there are several adverse effects associated with oral bisphosphonates including the bisphosphonate related osteonecrosis of the jaw (BRONJ). Several risk factors drug-related, local and sistemic factors have been linked to BRONJ. A more recent report described an absolute risk ranging from 0.46% to 0.99% among patients receiving oral bisphosphonates. In this paper, the osteonecrosis of the jaw associated with oral BP therapy in patients affected by osteometabolic disorders was reviewed in order to renew the current knowledge.
Materials and methods. Were observed 12 in 55 patients affected by metabolic diseases (36 cases of BRONJ in total observed), between 2010 and 2013, and treated with oral NBP. The patients were referred to our hospital for diagnosis and surgical treatment. Each patient was clinically examined and a detailed medical history was raised. The majority (8/12) were prescribed alendronate, 2 oral ibandronic acid; 1 a. risendronico; in 8 patients, the osteoporosis was associated with systemic risk factors as Diabete, Rheumatic disease, Hypothyroidism, Hepatitis C Virus Infection and supportive therapy (steroids and antiangiogenetic drugs). In 10 cases the duration of oral BP therapy exceeded 5 years (>5 -10aa.) prior to BRONJ diagnosis. The total of patients with concerning symptoms, received maxillofacial imaging (8 panoramic radiography; 1 computed tomography; 2 CBCT in the context of clinical care). The retrospective review of the clinical and surgical stage of BRONJ, was performed according to SIPMO - 2013 recommendations. Of the 12 patients, 8 cases were stage 1, 3 cases were stage 2 and 1 cases was stage 3. The surgical treatments were: 8 debridments, 3 marginal bony resections and 1segmental bony resection.

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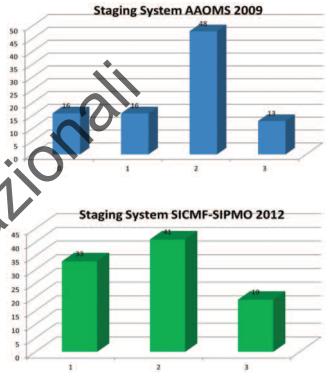
Category 1

What happens to the bronj patients when re-classified according to the novel SICMF-SIPMO recommendations? our experience



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Background. Since 2009, according to the American Association of Oral and Maxillofacial Surgeons staging system (AAOMS-SS), Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ) has been defined by the presence of bone exposition; in absence of this condition, patients presenting other unspecific clinical and/or radiological signs of disease were classified into the "stage 0". In 2012, the Italian Society of Maxillo-Facial Surgery (SICMF) and the Italian Society of Oral Pathology and Medicine (SIPMO) redefined BRONJ, as an adverse drug event, with several clinical forms (exposed and not-exposed), and updated the staging system, abolishing the stage 0. Aim of this study was to re-classify BRONJ cases in order to define the most adequate managements accordingly.
Method. A retrospective database analysis of BRONJ cases observed at the Sector of Oral Medicine-University of Palermo from 2005 to 2012 was performed. A total of 93 patients (M: 27; F: 66; mean age ± SD 69 ±7yy), previously classified according 2009 AAOMS-SS (stages 0, 1, 2 and 3), were reclassified according 2012 SICMF-SIPMO staging system (SS-SS) [stage 1(focal); 2(diffuse) and 3 (complicated)].
Results. In our sample, BRONJ AAOMS staging was the following: "stage 0"16/93 (17.2%); "stage 1" 16/93 (17.2%); "stage 2" 48/93 (51.6%) and "stage 3" 13/93 (14%). On the basis of the novel SS-SS, distribution of cases were: "stage 1" 33/93 (35.5%); "stage 2" 41/93 (44.1%) and "stage 3" 19/93 (20.4%). Of the 16 cases "stage 0", 6/16 (37.5%) has become "stage 1"; 6/16 (37.5%) "stage 2" and 4/16 (25%) "stage 3", respectively.
Conclusion. After the re-classification, a large quote of BRONJ cases, previously underestimated as stage 0, were properly diagnosed as diffuse-complicated cases. According to our experience, the updated staging system provide important clinical benefits, such as anticipating BRONJ diagnosis, performing therapies earlier and adequate to the correct staging, in order to increase treatment effectiveness.

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ONJ (osteonecrosis of jaw) in breast cancer patients: effect of preventive measures in a monoinstitutional experience

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Background. Breast cancer incidence was 114 cases on 100.000/year.
Bone is the most frequent site of metastases (mts) from breast and the presence of Skeletal Related Events (SRE) increases morbidity. The treatment is based on chemotherapy, endocrine therapy, radiotherapy and recently also target therapy agents (trastuzumab, lapatinib, bevacizumab, everolimus). These therapies are frequently associated with antiresorptive agents, such as Bisphosphonates (BPs), including Pamidronate, Zoledronic Acid, Ibandronate, or an anti-RANKL agent, Denosumab. All these agents are able to reduce the risk of SRE and to delay SRE onset. However they are associated with adverse events, including Osteonecrosis of Jaw (ONJ) that can occur in 1.1-9.9 % of breast cancer pts. Preventive (risk reduction) measures before BP and Denosumab treatment (dental visit, dental RX, eventual teeth extractions, dental and denture care) have been recommended.
Materials and Methods. We reviewed all breast cancer patients affected by bone mts observed by our team at the Oncology Unit in years 2005-2013. They were classified as: a) Hystoric group (pts already under BP treatment on 2005); b) Prevention group (pts undergoing preventive measures before BP therapy start); c) Screening group (pts treated with BP, not receiving prevention due to several reasons, on years 2006-2013).
Results. We followed 168 pts treated with BPs and/or Denosumab. ONJ was observed in 10/168 pts (5.9%). In the Historic group we observed ONJ in 6/60 pts (10%); in the Screening group in 3/24 pts (12.5%); in the Prevention group in 1/84 (1.2%).
Conclusions. The preventive measures can minimize the rate of ONJ and could potentially reduce the impact on Quality of Life in case of ONJ onset. Breast cancer pts that start BP and Denosumab without pre-treatment assessment (due to clinical emergency, etc) are at higher ONJ risk. Our experience data reinforce the literature recommendations about implementing preventive protocols.

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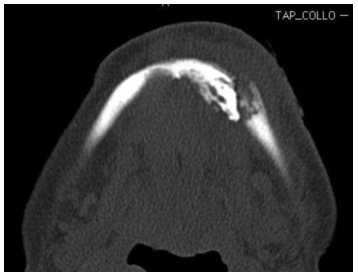
Pathologic fracture of the mandible due to BRONJ



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Up to now there are only limited data concernig incidence and management of pathologic fracture of the mandible due to bisphosphonate-related osteonecrosis of the jaw. We report a case of a 71 –year-old woman hospitalized in our Department with a diagnosis of left submandibular abscess and cutaneus fistula. Medical history of the patient revealed no major illnesses neither facial

traumas neither recent dental treatments. The patient was taking Fosamax®(alendronate sodium) for the treatment of osteoporosis from 10 years, orally 70 mg a week. A CT-scan showed area of bone sequestration and pathological fracture of the mandible and a diagnosis of BRONJ stage III was made based on the criteria of the American Association of Oral and Maxillofacial Surgery (AAOMS, 2007).
The patient underwent surgical treatment, consisting in: - extraoral-submandibular approach with excision of the fistula, - sequestrotomy with removal of necrotic bone parts and fracture reduction, - rigid internal fixation and mandibular reconstruction using a preformed reconstruction titanium plate. The surgery was supported by intravenous antibiotic therapy for one week, followed by orally administration for two weeks. During the follow-up period (22 month) was observed a good healing without exposure of the reconstruction plate and acceptable functional and aesthetical results. The pathological fracture represent the severest complication of BRONJ in the mandible, and seriously impairs the quality of life of the patient. Despite this, there are no therapy guidelines and surgical protocols are still controversial, ranging from conservative management up to radical bone resection with microvascular reconstruction. In our opinion, in the treatment of pathologic fractures of the mandible due to BRONJ, good functional and aesthetical results can be achieved removing the necrotic bone parts and performing a load-bearing osteosynthesis.

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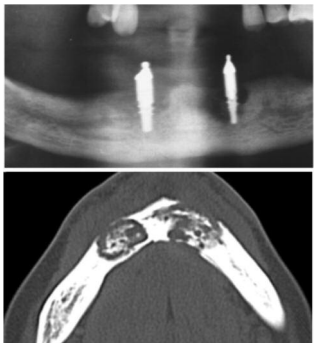
Case Report

Bisphosphonate-related osteonecrosis of the mandible after implant surgery



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According to current literature, a history of use of bisphosphonates is not an absolute contraindication for dental implant placement. BRONJ associated with dental implants is a rare complication and the few reports in literature have reached conflicting conclusions. Furthermore recent studies have indicated that the relative incidence of BRONJ in patients receiving bisphosphonates orally for osteoporosis treatment is higher than previously thought.
We report a case of a 70-year-old patient presented to our observation in April 2011 with an area of infected and exposed necrotic bone in the anterior mandible with two mobile dental implants. The patient underwent rehabilitation of the anterior mandible with two dental implants in December 2010 while taking Fosamax® (alendronate sodium, orally 70 mg a week from 2005) for the treatment of osteoporosis. A panoramic radiograph and CT scan showed an increased bone marrow density with large peri-implants bone sequestration (en block sequestration of bone with implant). A diagnosis of BRONJ stage II was made based on the criteria of the American Association of Oral and Maxillofacial Surgery. The patient was treated surgically following an intraoral approach. Sequestrectomy with removal of necrotic bone, removal of implants, osteoplasty and primary closure were performed. Orally antibiotic therapy followed for two weeks. At a 6-month follow-up control, there was no evidence of disease with a normal mandibular mucosa.
It has been stated that BRONJ associated with dental implants usually is a late complication unrelated to surgery and that generally affects the posterior sectors of the mandible. However, this case report highlights how the BRONJ associated with dental implants can be a devastating side effect of treatment with oral BPs, triggered by implant surgery. In our opinion, great care must be taken in the selection of patients and further studies are required to identify risk groups.

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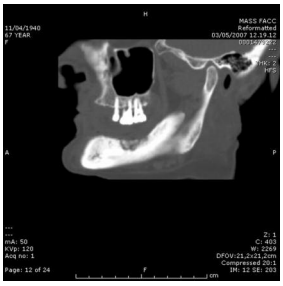
Category Chosen 2

Computed tomography (CT) diagnosis of unexposed osteonecrosis of jaw (ONJ): different aspects of 13 cases



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Background. "Unexposed bone variant" (patient with signs and symptoms of ONJ but without clear mucosal break and bone exposure) account for up 1/3 of all ONJ cases; these cases have been included in the so-called "stage 0" of the 2009 AAOMS staging system (1) and can cause underestimation of ONJ frequency in studies with adjudication based on AAOMS definition. Imaging exams (CT scan, bone scintigraphy, etc) are able to show real bone lesion involvement.
Material and Methods. We reviewed CT scan of ONJ patients, classified at the exam time as "stage 0" according to AAOMS; we registered the main radiological aspects of ONJ sites and (whenever possible) adjudicated the clinical-radiological stage according to the Italian SIPMO-SICMF staging system (2-3). CT scans of maxilla and mandible were performed by spiral multidetector (4-32 row) scanner.
Results. We examined 13 cases (14 ONJ sites): M/F 6/7 ; breast cancer / prostate cancer / myeloma / renal cancer 5/4/3/1. Site: 10 mandible / 2 maxilla / 1 both. CT pattern and stage by SIPMO-SICMF staging system: 4 sites showed focal sclerosis (alveolar region only), for 1 stage Ia and 3 Ib; 10 sites showed diffuse sclerosis (extra-alveolar region), with 4 stage IIa and 6 stage IIb; no alteration such as mandible fracture, skin fistula, sinus tract (classified as stage III) was detected. Other figures: a bone sequestrum was identified in 7 cases, maxillar sinus involvement in 1 case, periosteal reaction in 3, soft tissue alterations in 3.
Conclusions. Unexposed ONJ cases (so-called "stage 0") can show variable grades of CT alterations with possible impact on case management and treatment strategy. CT scan is strongly recommended in case of clinical suspect of ONJ without bone exposure.

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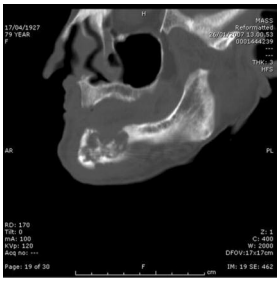
Category Chosen 2

Mandible fracture and other complications due to osteonecrosis of jaw (ONJ): CT aspects of 4 advanced cases



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Background. Complicated and severe ONJ cases are collected in the stage III of clinically based 2009 AAOMS staging system (1); possible signs are mandible fracture, skin fistula, sinus or nasal tract. Computed Tomography (CT) scan is able to show real bone lesion involvement, beside the only clinically detectable signs.
Material and Methods. We reviewed CT scan of ONJ patients, classified as stage II and III according to the clinical AAOMS staging system, and we classified them according to Italian SIPMO-SICMF clinical-radiological staging system (2-3), looking for the main radiological aspects of advanced cases (stage III). CT scans of maxilla and mandible were performed by a spiral multidetector (4-32 row) scanner.
Results. We reviewed 35 "staging time" CT scans (of 32 ONJ patients). There were 4 advanced cases: M/F 2/2 ; disease was breast cancer (1), prostate cancer (1), renal cancer (1), osteoporosis in Rheumatoid Arthritis (1). Site: 2 mandible, 1 maxilla, 1 both. All 4 cases were stage III in both staging systems. CT aspects: 2 patients showed mandible fracture, 3 cutaneous fistulae, 2 maxillary sinus involvement, 1 extension to nasal bone, 2 presence of a sequestrum or bone fragments, 3 soft tissue involvement.
Conclusions. CT scan is strongly recommended in case of clinically advanced ONJ to adequately evaluate bone extension and involvement and to plan treatment.

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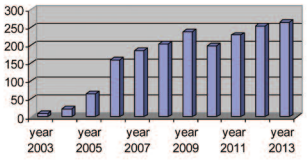
Category Chosen 2

Osteonecrosis of jaw (onj) 2003-2014: analysis of literature reporting



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Osteonecrosis of the jaw (ONJ) is a serious adverse event of drug treatment. ONJ was observed mostly in patients suffering from multiple myeloma or bone metastatic cancer receiving intravenous bisphosphonates (BPs), and, to a lesser extent, in non-cancer patients treated with oral BPs. Recently, ONJ has also been reported in patients receiving denosumab and in those treated with antiangiogenic agents. After first reports on years 2003-2004, an explosion of papers appeared in literature sources, mostly with intent of reporting single cases or case series, or describing general aspects of ONJ disease.
Materials and Methods. We reviewed presence of papers published on PubMed since 2003 to March 2014. Automatic searching for "Osteonecrosis AND (jaw OR jaws)" was implemented as a proxy for ONJ; further manual search was made with other key words.
Results. We obtained 2047 papers from automatic search, of which 1923 after 2003, mostly about ONJ related to BPs or other drugs. From 10 in 2003 and 22 in 2004, we registered a fast increase: from 65 in 2005, to 160 in 2006, 186 in 2007, 204 in 2008, 238 in 2009; afterwards we observed a plateau (198 in 2010, 229 in 2011) and then a new increase: 253 in 2012, 262 in 2013, and 96 in first 3 months of 2014. We classified papers as follows: case reports and clinical experiences (32%), reports of behavior or therapeutic protocols, including surgery (38%); literature reviews (20%); animal model and basic science (7%); guidelines and recommendations about preventive measures (1%); cost-effectiveness and economics (<1%). On years, we observed a clear increase of papers reporting specific aspects: imaging; clinical behavior and disease history; preventive, or risk reduction, measures; treatment; animal models and base science research.
Discussion. Some points are to be elucidated and need urgent research reports: comparative evaluation of treatment options (conservative versus surgical, etc); evaluation of response to treatment (outcome research); long-term Quality of Life assessment.

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Category Chosen 2

Is preventive oral health care sufficient to avoid bisphosphonate-related osteonecrosis of the jaw? Apropos of an atypical case

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Introduction. We present the case of a patient preventively evaluated, with complete tooth removal before intravenous (IV) bisphosphonates (BF) administration, developing osteonecrosis of the jaw (ONJ) at follow-up.
Methods. Patient was admitted to our clinic in order to obtain a preliminary evaluation before IV BF administration for metastatic lung cancer. His oral health care was clinically and radiologically evaluated and need for complete tooth removal was then stated. After tooth extractions the patient was scheduled for regular follow-up.
Results. Forty days after oral surgery, clinical oral healing was reached and intravenous bisphosphonate drugs administration was started. The patient received intravenous administration of zoledronic acid 4mg every 28 days, four times, then stopped for ONJ onset.
He presented at five-month follow-up with painful exposition of the alveolar bone in left lower molar region.
Many attempts of conservative management were made. For 7 months he received multiple cycles of alternated oral and intravenous antibiotics; periods of pain remission and recurrence alternated, with permanent and worsening oral bone exposure. A bony sequester slightly developed, as demonstrated by radiological findings.
Then a severe left lower jaw and upper neck phlegmon compared, so intravenous antibiotic therapy was newly started; few days later the patient underwent surgery for sequestrum removal, bone curettage and local debridement under general anaesthesia. At three-month follow-up, no pain neither further bone exposure recurred.
Discussion. The importance of scheduled long-term follow-up is pointed up, even in patients with preventive evaluation and complete tooth removal without any apparent oral disease hazard. Many trouble may occur and patients must be quickly and wisely treated. Surgery in ONJ is indicated only in selected cases, when conservative treatment fails to provide satisfactory results.

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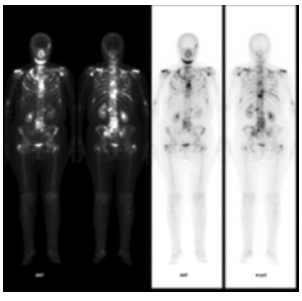
Case Report

Scintigraphy as a predictive tool in bronj: a case report



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Bisphosphonates treatment carries an increased risk of developing osteonecrosis of the jaws, which can occur either spontaneously or as a consequence of surgical procedures or infections.

This report is about the case of an 82-year old woman who came to our attention in 2011. Comorbidity were: HCV positive, insulin-independent diabetes and metastatic breast cancer.
The patient was sent to our department to be evaluated before starting Zoledronic acid infusions: we detected total edentulism on both arches and the presence of two implants in the places of 33 and 43; no mucosal lesions or infective processes were detected and the patient was allowed to start bisphosphonates therapy.
Clinical examination remained unremarkable up to April 2013 when the patient presented with a peri-implant abscess at 43: abutment removal was performed and antibiotic therapy (amoxicillin and clavulanic acid) was initiated. Subsequence evaluation revealed an apparent resolution of the infection.
In May 2013 total body scintigraphy was performed and revealed areas of increased uptake also in the mandible despite the absence of clinical signs of infections.
In July 2013 the presence of cutaneous fistulas was observed and Cone Beam/CT and MRI were performed: CT and MRI confirmed findings that suggest ONJ diagnosis.
On 7 November 2013 segmental resective surgery of the necrotic bone was carried out.
It is important to stress that total body scintigraphy revealed, in this case, the presence of lesion before clinical signs were evident: this seems to support the idea that scintigraphy may provide useful data for early diagnosis, even in the cases in which is not detectable intraoral bone exposition.

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Case Report

Experience of a documentation center for osteonecrosis of jaw (ONJ) data collection

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The ONJ is a recently (since 2003) recognized disease reported in association with use of bisphosphonates (BP) in oncologic, hematologic and osteoporotic patients. Not all clinicians are aware of ONJ epidemiology, risk factors, treatment, preventive measures. On 2005, oncologists and haematologists together with other specialists, nurses and data managers, founded a multidisciplinary team for study, treatment and prevention of ONJ at Alessandria Hospital (North-Western Italy). This group launched the idea of a Documentation Centre about Osteonecrosis (Centro Documentazione Osteonecrosi) whose activity was planned to be useful to both professionals and patients. The activities of the Centre included collaboration with doctors and health professionals working in whole Italy to extend a common diagnostic pathway and a prevention strategy of ONJ. One of the most important activities of the Centre is the collection and classification of all published issues on the topic (since 2003), both from scientific journals, and from other sources (ie, internet). Other data are collected by contacts with experts, research centres and health professionals dealing with the issue, in order to create a complete and detailed archive (updated monthly). Documents are sent, upon request, to healthcare professionals all over Italy.
The Centre has also collaborated at activities of the Working Group on ONJ within the regional Oncology Network (Rete Oncologica) of Piemonte and Valle d'Aosta: from a register of ONJ cases seen in more than 30 hospital centres, to the development and diffusion of a data collection sheet, to cooperation with the Oncology Network Study Group that drafted the "Recommendations for the use of BPs in cancer patients" (2012).
The Centre plays also a role of consultancy activities (by e-mail and by phone) for physicians, dentists and patients asking for information about the issue. The Centre is continuously involved in organizing national and regional conferences.

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Teriparatide therapy for alendronate-associated osteonecrosis of the Jaw: our experience on three cases

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Objective. Teriparatide is a synthetic polipeptidic hormone, which contains the amino-acidic fragment of the 1-34 parathyroid recombinant hormone (rhPTH 1-34). Pulsatile exposure to lower doses actually results in increased bone mineral density (BMD) and bone mass. The off-label use of Teriparatide in BRONJ patients affected from osteoporosis has recently been reported in literature.
Methods. Three patients affected from BRONJ assuming Alendronate for osteoporosis were referred to our clinic. Before starting therapy with teriparatide (Forsteo 20μg 1 f sc/die) patients underwent spine x-ray, complete blood count, serum protein electrophoresis, determinations of serum calcium, creatinine, phosphorus, alkaline phosphatase, uric acid, alkaline phosphatase, TSH, PTH, and 24-h urinary calcium.
Ortopantomography was performed at time 0, 3 and 6 months; CT at time 0 and 6 months. Clinical controls were performed every 2 weeks.
Results. One patient had a rapid improvement of symptoms, but surgery was needed to complete healing. In the second case a complete healing occurred. In the third case symptoms rapidly improved nevertheless, surgery would be needed for the persistence of bone exposition but it was not performed due to the medical condition of the patient.
Conclusions. In all these cases teriparatide brought to resolution of pain and, in two patients, of the BRONJ lesions. However, the rapidity of response suggests that a rigorous evaluation of teriparatide in a RCT would be of interest in patients with osteonecrosis of the jaw who have been taking bisphosphonates.

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ONJ (osteonecrosis of jaw) in osteoporosis patients after ibandronate treatment: report of two cases

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In cancer patients, ibandronate - also known as ibandronic acid - is administered to breast cancer patients and other patients suffering bone metastases (Bondronat ® monthly 6 mg IV infusions, or daily 50 mg tab); in cancer patients ibandronate has been hypothesized as conferring a lower ONJ risk in comparison with zoledronic acid .
Ibandronate is also administered, with different schedules and doses (Bonviva ® 3 mg IV vial, once every 3 months; or 150 mg tab, once per month) to osteoporotic patients. Few cases of ONJ related to ibandronate in not-cancer pa-

tients have been reported so far in literature. We report here two cases of female patients recently referred to our hospital ONJ multidisciplinary team.

Case 1. Female, 57 years old, admitted on January 2012. She had received ibandronate for 36 months (150 mg/month orally), till December 2011. On November 2011 she was submitted to tooth extraction with persisting alveolar socket. On December 2011 she complained pain at left hemi-mandible, resolved after antibiotic therapy. We found exposed bone at left hemi-mandible. CT scan showed mandible lesion with presence of sequestrum. Bone scan (Tc 99 scintigraphy) revealed left mandible uptake. Follow-up is on-going.

Case 2. Female, 78 years old, referred to our team on September 2013. She had received oral ibandronate (150 mg tab) for 22 months. On 2009 she was submitted to insertion of mandible implants. On September 2013 she complained mandible pain. We found exposed bone next to implants. CT scan showed large mandible lesions. She refused surgical treatment.

Comment. Osteoporotic patients receiving ibandronate have to be closely monitored for ONJ risk.

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Case Report

Metachronous sites of osteonecrosis of jaw (ONJ) in all four quadrants of maxilla bones and mandible: a case report

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Osteonecrosis of Jaw (ONJ) after treatment including Bisphosphonates (BPs) is often multifocal, involving several sites of maxilla and/or mandible in the same time (synchronous) or in different times (metachronous). We report the case of metachronous involvement of all four jaw quadrants, after zoledronic acid treatment of breast cancer with bone metastases.

Case description. At age of 72, on November 2010, a female patient received surgery for breast cancer. A bone scan (Tc99 scintigraphy) revealed diffuse bone metastases, treated with chemotherapy, endocrine therapy and radiotherapy. After first courses of chemotherapy, since March 2011, she was submitted to preventive extractions of not salvageable teeth. She started zoledronic acid therapy on July 2011 (>2 months after last extraction). On October 2011, a diagnosis of ONJ was made at left hemi-mandible (at an extraction site), with CT lesion and bone scan uptake; a spontaneous sequestrum expulsion was referred by the patient. Zoledronic acid therapy was resumed but right hemi-mandible pain began and a bone exposure appeared.

In the following years (2012 and 2013), bone scan uptakes appeared at right and left maxilla: only after some months, CT lesions appeared and inflammatory events were registered at those maxilla sites.

Discussion. History of ONJ in a patient treated with BPs makes automatically the patient at risk of other ONJ sites; short-term follow-up examination is needed during following months and years, whether BP treatment is resumed or not, to avoid diagnosis delay of new ONJ sites and possible complications. Careful evaluation of routine bone scans (Tc99 scintigraphy) can anticipate symptoms and clinical signs from new ONJ sites. Eventual Rx exams (orthopanotogram) and/or CT scans in patient at high risk of multifocal ONJ disease can be useful beside the value of follow-up evaluation of known sites; pros and cons of eventual partial vision procedures (such as cone beam CT) have to be evaluated in patients with known ONJ sites due to risk of missing early diagnosis of multifocal disease.

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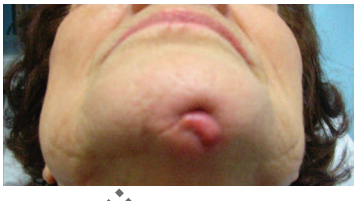
Case Report

Osteonecrosis of jaw in rheumatoid arthritis patients receiving Oral Bisphosphonates: Not always an event of moderate severity



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Recent literature show that Rheumatoid Arthritis (RA) patients are prone to develop Osteonecrosis of Jaw (ONJ) after therapy including Bisphosphonates (BPs), mainly oral (alendronate, risedronate, ibandronate) as treatment or prevention of osteoporosis. Charts of 8 ONJ cases in not-cancer patients referred to our hospital ONJ multidisciplinary team were reviewed; 3 out of 8 cases were in RA patients.

Case 1. Female, 66 years. Treated with clodronate (2 years) and risedronate (5 years). After tooth extraction, right mandible lesion; submitted to two surgical procedures along years.

Case 2. Female, 80 years. Treated with alendronate for 4 years. Mandible lesion (after extractions and denture trauma) with cutaneous fistula.

Case 3. Female, 73 years. Treated with alendronate for 9 years. Referred to our team after one year of pain and suppurated lesion in right mandible (following tooth extraction); spontaneous sequestrum expulsion.

Discussion. The proportion of RA patients among ONJ cases in osteoporosis (not cancer) patients seems higher than in general population receiving oral BP, so that RA patients could be considered at higher ONJ risk. Possible reasons of this high risk (RA itself; steroid therapy; long term oral BP therapy; immunosuppressive and other biological agents) are to be fully explored. The clinical outcome and history of ONJ in general oral BP treated population is often reported as indolent, not severe and diagnosed in not advanced stages; this is not the case of ONJ in RA patients, with even life-threatening disease reports. Our ONJ cases in RA patients showed advanced disease, less manageable than that one detected in ONJ cases related to oral BP in osteoporotic patients without RA.

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Case reports

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) due to badly-fitting dentures: a retrospective study

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Aim. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is an adverse drug reaction described as a progressive bone destruction and necrosis affecting the jaws of patients exposed to the treatment with bisphosphonates (BPs) for bone disorders such as osteoporosis, or osseous metastasis and multiple myeloma. The study aims to contribute to the acquisition of a greater awareness of the problem for the physician and the dental surgeon both.
Methods. A retrospective study on 33 patients referred to the Hospital in San Giovanni Rotondo between 2007 and 2013 was performed. The following data were recorded and entered into a database: gender, age, primary disease, comorbidity, site, trigger, symptoms, size, stage, type and duration of BPs therapy. Out of 33 patients, 17 presented BRONJ after avulsion, 6 showed BRONJ related to removable dentures, only 3 cases were related to a prosthetic bridge, and in 7 cases the trigger was not detectable.
Results. All 9 patients with BRONJ related to prosthesis were treated with intra-venous zolendronic acid 4mg/month. Six patients were female suffering from breast cancer, and three were males, suffering from prostate cancer. The mean age in our sample was 76.89±10.49 years (range 63 to 94 years), and the mean duration therapy was 25.44±6.46 months (range 15 to 36 months). All patients reported badly-fitting dentures making gingival trauma and hence inflammation and swelling.
Conclusions. According to our experience the general attitude of the clinician must be cautious, considering frequent dental check-ups for patients taking BPs. Maximizing oral hygiene and reducing risk factors are necessary, because also prosthetic problems leading to trauma to the overlying soft tissues may lead to BRONJ. Most of the authors report a higher percentages of spontaneous cases, but this may be due to the fact that it is difficult to establish the initiating factor in some patients, and many of the 'spontaneous' cases are due to ill-fitting dentures.

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Case Reports

A case of Er:YAG laser-assisted treatment of bisphosphonate-related osteonecrosis of the jaw (BRONJ)

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Introduction. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a severe side effect of bisphosphonates therapy.
Case report. A 84-year-old woman came to us with paresthesia/anesthesia of the left submental region and the presence of a fistula in the third quadrant. Despite the extraction of 3.7 was performed 3-months before, OPG showed the presence of non-healing extraction site associated with bone rarefaction, mimic classic osteomyelitis.
The patient, affected by postmenopausal severe osteoporosis, had 1-year history of monthly orally administered ibandronate (150 mg). Any story of radio or immunosoppressive therapy was reported.
After antibiotic therapy (amoxicillin-clavulanic acid 1g bid and levofloxacin 500 mg bid for 10 days) and 0.2% chlorhexidine rinses (tid) administration, an Er:YAG laser 2940 nm (80/250 mJ, 20 Hz, VSP mode, 600 μm fiber, water irrigation) was used to performed a mucoperiostal flap and then to remove the necrotic bone, under local anaesthesia with 3% carbocaine. A complete closure of the surgical wound was performed through 4/0 silk continuos sutures and the use of total denture was forbidden for 15 days. Oral spiramycin (3M U.I. bid) and 0.2% chlorhexidine rinses (tid) for 15 days was prescribed. Soft and cold diet for 2-3 days was recommended.
The histological examination showed micro areas of necrosis alternated with remarkable lymphoplasmacytic infiltrate; the BRONJ diagnosis was confirmed.
After 15 days the suture was removed. At 45 days follow-up the sensibility of the left submental region was restored and a complete soft tissue recovering was achieved. At 6 months follow-up, soft tissue healing was maintained without symptom recurrence and CT showed signs of trabecular bone reconstruction.

Conclusion. In according with the literature, the association of antibiotic therapy and Er:YAG laser surgery can be effective in treatment of BRONJ, with reduction of intra-operative bleeding, post-operative pain and healing times.

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Case reports

ONJ (osteonecrosis of jaw) after short-term treatment with sunitinib and bisphosphonates In a renal cell cancer patient

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Renal Cell Cancer (RCC) patients receiving Bisphosphonates (BPs) seem at higher risk for Osteonecrosis of Jaw (ONJ) after introduction of targeted therapy (biological agents as bevacizumab, sunitinib, mTOR inhibitors, etc). The higher ONJ risk could be linked: a) to anti-angiogenic effect of both BPs and targeted agents, and/or b) the prolonged survival of RCC patients (due to targeted therapy) and then prolonged drug exposure. We report the case of a RCC patient developing ONJ after a short-term treatment of BPs and targeted therapy.

Case description. Male, 56 years old: on November 2012, diagnosis of renal carcinoma and diffused metastases (brain; chest and abdomen lymph nodes; lungs; bones). On December 2012, BP therapy (zoledronic acid) and bone radiotherapy were started due to clinical emergency, without any preventive dental visit; immediately after, he started also targeted therapy (sunitinib). On January 2013, zoledronic acid was replaced by ibandronate. After some months, he showed good response at level of brain, pulmonary, renal, lymph nodal, bone metastases; he was also surgically stabilized at left femur. On June 2013, he complained pain at right maxilla; ibandronate therapy was suspended and the patient was submitted to extraction of a mobile unsalvageable tooth. On October 2013, he complained right maxilla pain, with pus and blood discharge: a right maxilla bone exposure was present. A maxilla and mandible CT scan revealed several bone lesions, some of them probably of neoplastic nature and some others resembling ONJ lesions. A conservative treatment of ONJ was adopted.

Take home messages. 1. In RCC patients, targeted agents are very useful and can prolong survival even in case of very advanced disease. 2. Bone metastases and ONJ lesions can coexist in jaws. 3.Was the extraction an ONJ trigger, or was the unsalvageable tooth a sign of an underlying unknown ONJ disease? 4. ONJ lesions can occur after short-term therapy including BPs and targeted therapy; RCC patients are to be carefully monitored.

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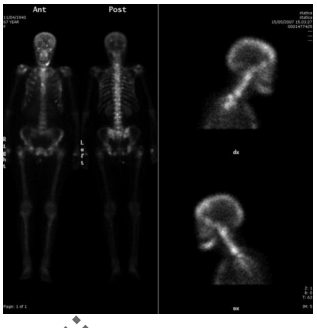
Adjunctive role of bone scan (tc99 scintigraphy) for diagnosis of exposed and unexposed osteonecrosis of jaw (ONJ)



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Background. The literature regarding the role of ^{99m}Tc-MDP bone scan (BS) in the diagnosis of bisphosphonate (BP)-related ONJ is limited and unconsistent. BS is an imaging technique with high sensitivity for bone turnover alterations, routinely performed in most of patients with skeletal metastases at diagnosis and at periodic evaluation of treatment effect. BS has low specificity (uptakes due to metastases, as well as bone traumatic, inflammatory, degenerative lesions). In osteoradionecrosis patients, bone necrosis (sequestrum) can appear at BS as a downtaking area surrounded by an uptaking area, but uptake is the predominant figure in BP-related ONJ. We hypothesize that jaw BS uptakes could be an useful sign to make or confirm an ONJ diagnosis (especially in patients without bone exposure), and could be useful in follow-up of ascertained ONJ cases.
Methods. We conducted a retrospective study of BS performed in 19 ONJ patients treated with BPs (11 females with breast cancer, 1 male breast cancer, 7 prostate cancer patients). Two Nuclear Medicine specialists reviewed 17 BS performed at the diagnosis time of ONJ (or within 3 months), and 13 BS collected after the diagnosis of ONJ (follow-up procedures).
Results. At the moment of ONJ diagnosis, 14 out 17 evaluated procedures resulted as "positive" (evident uptake in ONJ site) and 3 were "doubtful" (moderate uptake). Of particular interest, 5 of 6 cases of unexposed ONJ (stage 0 according to AAOMS) were positive and 1 doubtful. At follow-up evaluations, BS uptakes changed either towards reduction or towards increase of intensity (probably due to osteomyelitic disease and related treatment). Persistence of uptake was noted even in case of apparent ONJ remission (closure of oral mucosal break).
Conclusions. These retrospective data will be used to design a case-control study with different patient groups, inluding ONJ cases, patients treated with BPs and not suffering from ONJ, and cancer patients not receiving BPs.

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Osteonecrosis of jaw (ONJ) in renal cell cancer patients: an emerging problem

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Background. Osteonecrosis of the jaws (ONJ) associated with the use of bisphosphonates (BPs) has been rarely reported in metastatic renal cell cancer (RCC) patients, in first years of ONJ reporting (2003-2007). In recent years the prognosis of advanced RCC patients has greatly improved, due to the development and registration of novel targeted agents: Tyrosine Kinase Inhibitors (TKIs), such as sunitinib, sorafenib, and pazopanib; an anti-VEGF agent, bevacizumab; mTOR inhibitors: temsirolimus and everolimus. Since the introduction of combined therapies consisting of BPs and targeted agents, an increasing number of RCC patients were reported to develop ONJ, suggesting that therapeutic angiogenesis suppression may increase the ONJ risk in BPs users; ONJ was rarely observed even in RCC patients receiving targeted agents alone, mainly Sunitinib (ref 1-2). On November 2010, EMA (European Medicine Agency) issued safety warnings about ONJ risk during Sunitinib or Bevacizumab treatment; in consequent "dear doctor" alert letters, manufacturers reported few ONJ cases worldwide.
Material and Methods. We reviewed literature data (PubMed and other sources) looking for papers reporting ONJ cases in RCC patients, after combination of BPs and targeted therapy or targeted agents alone. We also asked Authors of papers for individual patient data, if not published: age; sex; BP type and duration of treatment (at the time of ONJ diagnosis; targeted agent type (at the ONJ onset) and duration of treatment; other targeted agents previously employed; ONJ site; presence of known risk factors for ONJ.
Results. We reviewed 20 studies (papers or abstracts, from 9 different countries), registering details of 31 RCC patients suffering of ONJ after BP and targeted therapy (26 cases) or targeted agent alone (5 cases). Further 44 ONJ cases in RCC patients were registered in nine Italian centres in a recent collaborative study (ref 3).
Conclusions. ONJ in RCC patients is an emerging problem, underestimated in current literature.
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Category 2 B

Osteonecrosis of the jaw in a patient treated with zoledronic acid and everolimus: a case report

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Longer treatment duration and greater cumulative doses of bisphosphonates have been associated to higher risk of developing bisphosphonate related osteonecrosis of the jaw (BRONJ)[1]; but up to now there are no information about the discontinuation of bishosphonate therapy and the occurrence of osteonecrosis. Recently osteonecrosis of the jaws has been also reported in cancer patients treated with targeted agents such as denosumab, anti-angiogenic drugs (sunitinib, bevacizumab) and everolims (inhibitor of mammalian target of rapamycin mTOR).
In May 2010 a 65 years old man with bone metastasis from kidney cancer was referred to our department before starting treatment with zoledronic acid; clinical examination and panoramic x-ray were performed. He was included in our follow-up program and received zoledronic acid 4mg iv monthly from October 2010 to December 2010 and from January 2013 to March 2013; concomitant therapies were sunitinib 50mg/die for 4 dosing cycles from July 2010 to January 2011 and everolimus 10mg/die from November 2012 to April 2013. No symptoms or signs of ONJ were detectable till July 2013 but in December 2013 he presented for pain and swelling: an area of exposed bone was present in the mandibula (figure 1); other two ONJ sites were detected in the maxilla. No extractions were performed since the first visit and no local precipitating factors were identified; antibiotic therapy managed the abscess but no substantial changes in the necrotic exposed zone occurred.
Persistent bisphosphonate effects on bone after stopping therapy are known; a long bone half-life, up to 10 years, has been reported[2]. The role of antiangiogenic drugs and everolimus associated to bisphosphonates in promoting osteonecrosis of the jaw is still not clear[3]. Follow-up after suspension of bisphosphonates therapy is recommended and the new targeted cancer therapy should be considered as potential additional risk factors.
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Category 2 B

Lack of prevention and life threatening

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FIGURA Cat2B_fig2

Bisphosphonate related osteonecrosis of the jaw (BRONJ) is often refractory to therapy and sometimes progressive; its clinical course varies depending on different factors[1] and long term prognosis is still difficult to make. There is consensus among the experts on the importance of prevention by reducing dental risk factors and maintaining oral health, regular monitoring of such patients is recommended[2].
In December 2013 a 61 years old woman with multiple myeloma presented in the emergency service of our unit complaining pain and swelling of her face. She was also affected by insulin dependent diabetes and was in anticoagulant therapy. The clinical examination revealed an important swelling in the right side of mandible, spreading to the neck, with a cutaneous fistula and in the same side of oral cavity a wide area of exposed bone on the inferior edentulous ridge. The patient was immediately admitted to hospital; two drainage from the neck and finally right hemimandibulectomy were performed.
The patient had been evaluated in our unit with panoramic x-ray before starting therapy with zoledronic acid in November 2009; follow-up was suggested but the patient never presented. She received zoledronic acid from December 2009 to April 2011 and an autologous bone marrow transplantation in May 2010. No extraction were performed. From April 2011 her multiple myeloma was in remission with normal blood tests (last one in October 2013) and no cancer therapy was necessary but steroid therapy 2mg/die. In March 2013 she was still in intensive care for the septic complications of BRONJ (Fig. 1).
The pathogenesis of BRONJ is complex and multifactorial; dental practitioners should carefully consider comorbidity status as a risk factor[1,3]. With unpredictable outcome and no standard treatment for BRONJ it’s really important for cancer patients treated with bisphosphonates to be regularly evaluated by a multidisciplinary team including the dental practitioner[1,2].

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Category 2 B

Thirty-eight cases of bisphosphonate-related osteonecrosis of the jaws

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For thirty-eight patients (16 males, mean age of onset lesions 69.31±SD 8.73, min 51.66–80.83; 22 females, mean age 67.76±9.53, min 43.25–max 82.41) with bisphosphonate-related osteonecrosis of the jaw (BRONJ), gender,

age, underlying diagnosis, type of bisphosphonate (BP), administration route and duration, location and stage of osteonecrosis, symptoms and oral health status, radiological findings, treatment and outcome, were recorded.
Underlying diagnoses in the series were: 17 multiple myeloma, 7 breast cancer, 5 prostate carcinoma, 2 kidney cancer, 1 lung/bladder/mediastinal cancer, 1 chronic lymphocytic leukemia, 1 osteoporosis, 1 palatal osteosarcoma+osteoporosis, 1 non-Hodgkin's lymphoma.
Fifty-seven osteonecrotic lesions were detected 36 localized in the mandible, 21 in the maxilla; trigger events was tooth extraction in 40 cases (70.2%), periodontal disease in 4 (7%), incongruous dentures in 3 (5.3%), perimplantitis in 1 (1.75%), unknown in 9 (15.75%).
Thirty-six patients had received treatment using amino bisphosphonates (26 zoledronate, 6 pamidronate and zoledronate, 2 pamidronate, 2 alendronate),1 clodronate and 1 clodronate and ibandronate; the administration route was intravenous in 33 patients, oral in 2, intramuscular in 1 and intramuscular and oral in 1.
Mean number of doses to bone exposure for patients was 22.44 $\pm$ 14.70 for zoledronate, 48.33 $\pm$ 14.47 for pamidronate and zoledronate, 32.50 $\pm$ 44.55 for pamidronate, 146 $\pm$ 161.22 for alendronate, 500 for clodronate and 77 for clodronate and ibandronate.
Among statistical data the only significant finding was: the panoramic dental radiography gave no concrete support for diagnosis of ONJ lesions ($p \leq 0.04$); the mean values of plaque index (PI 2.23 ± SD 0.42) and gingival index (G.I. 2.38 ± S.D. 0.36) had values higher than those (PI 1.56±S.D. 0.94; GI 1.51±S.D.0.78, p=0.037 and p=0.003) detected in a sample of subjects of the same age treated with bisphosphonate but without osteonecrotic lesions.

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Category 2 B

Rat models of osteonecrosis of the jaws: an update

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An animal model is essential to investigate the pathophysiology of BRONJ and to explore prevention and management strategies to be tested subsequently with clinical trials[1]. Even if thirty years ago Gotcher and colleagues reported areas of necrotic alveolar bone protruded and exposed in the oral cavity in rats treated with dichloromethylene diphosphonate[2], only in the last five years different animal models, particularly rodens, were used to study the association between osteonecrosis of the jaws and bisphosphate (BF)[3]. Rats are the most used animals because they present several advantages: are easy to manage with, allows experimental protocols with high number of animals and the process of bone healing after tooth extraction is well known. On the other side some disadvantageous aspects are evident: the healing capacity of rodens are higher compared to human beings and the small dimension of these animals make the oral surgical procedures more difficult.
The aim of this study was to critically review the recent literature on BRONJ in rat models.
Relevant articles were retrieved from MEDLINE/Pubmed database and by hand-searching in bibliographies. Thirty seven studies published from February 2009 to March 2014 were selected.
The incidence of BRONJ in rats treated with BF ranges from 0 to 100% depending on different factors: BF exposure (type, doses, duration), surgical trigger events (tooth extraction, implant insertion, creation of soft tissue surgical wound or surgical bone defect), systemic co-factors (diabetes, vit D defiency), local infection (periodontitis, periapical infection) and associated drugs (corticosteroids, antibiotics, teriparatide). Some preventive strategies tested gave promising results.
The analysis of the literature demonstrate that BRONJ in rats, like in humans, is mainly associated with high potency amino BF combined with dento-alveolar surgical events and/or other predisposing factors, in particular corticosteroids.

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Category 2 B

A BRONJ stage 3 in a osteoporotic patient after 10 years of BPs discontinuation without risk factors

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The association between ostenecrosis of the jaws and bisphosphonate (BP) has been currently accepted only for nitrogen-containing BF, such as zoledronate, pamidronate and alendronate[1]. Even if some reports of BRONJ occurred after non-amino BF therapy[2] and a rat model of osteonecrosis of the jaws associated with clodronate have been published[3], the available clinical recommendations for patient treated with such BF does not differ from the standard protocols of oral health[1]. We report a case of stage 3 BRONJ developed many years after a cycle of e.v. infusions of clodronate for osteoporosis. The patient, a woman of 61 years old, was referred by her dentist for a poorly symptomatic alveolar bone exposition in the left posterior maxilla.
The elements 26 and 27 were extracted some months before and the medical history was positive for metabolic syndrome, osteoporosis, dyslipidemia, diabetes type II, autoimmune thyroiditis and hypertension. The patient reported a cycle of 10 infusions of clodronate (Ossiten ®300 mg) 10 years before and denied any current or previous therapy with corticosteroids.
Clinically the post-extractive alveolar sockets of 26 and 27 were exposed and clearly necrotic. TC scan showed the left sinus involvement. A provisional diagnosis of BRONJ was made. The patient was treated with antibiotics, sessions of low level laser therapy and the surgical removal of necrotic bone and the closure of the secondary oro-antral communication was performed. The histopathological evaluation of the bone sequestrum confirmed the diagnosis of BRONJ.
The peculiar aspects of this case are several: the necrosis was likely associated with a non-amino BF, currently non considered at risk for osteonecrois of the jaws; the BF was infused 10 years before the bone exposure; no other evident risk factors were present, excluding a well compensated (HbA1c 6,3%) diabetes type II.
We believe that further researches investigating the association of BRONJ with non-amino BF are needed.

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Category 2 B

Osteonecrosis of the jaws related to corticosteroids therapy: a case report

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Osteonecrosis of the jaws (ONJ) is a painful non-specific necrotic bone lesion characterized by a slow progression and incapability of spontaneous healing[1] with incapability to heal spontaneously. The most commonly described etiologic factor is radiotherapy of the head and neck region, osteoradionecrosis.
In recent years a progressive increase of osteonecrosis lesions in patients undergoing chronic therapy with intravenous BPs has been thoroughly manifested. BP-related osteonecrosis of the jaws (BRONJ) has been clearly de-

fined as a clinical scenario characterized by 3 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.

We present a case report of osteonecrosis unrelated to bisphosphonate therapy linked to corticosteroids therapy.

Clinical data. A 50-year-old male patient was referred to our clinic for a post-extractive non-healing lesion characterized by exposed bone. The subject underwent a single extraction of mandibular left second premolar, 3 months before attending our clinic.

Systemically the subject was positive for hypertension, hypothyroidism and psoriatic arthropathy. The patient denied any history of smoking. The patient reported also a previous therapy with prednisone 7,5 mg/day for two years finishing two months before extraction. He denied any usage of BPs or radiotherapy.

Clinically, the patient exhibited an area of exposing bone involving the premolar region of the left mandible. A panoramic radiograph (Figure 1) taken at the time of initial consultation showed an area of sclerosis, localized in the left mandible, involving the mental foramen. Treatment consisted of surgical debridement of the mandible, under local anaesthesia. After 30 days the area showed almost a complete recovery of the mucosa. The patient showed no symptoms or complain.

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Category 2 B

Bisphosphonate-related osteonecrosis of jaw (ONJ) in a male breast cancer patient receiving zoledronic acid: a case report

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Men are a minority of breast cancer patients (in Italy estimated new cases on 2013: 46900 female and 1100 male). Male breast cancers can develop bone metastases, frequently treated with antiresorptive agents: bisphosphonates (BPs) and denosumab. At our best knowledge, no case of ONJ in male breast cancer patient has been published so far. **Case report.** A male 53 years old patient came to observation of our hospital ONJ Multidisciplinary Team. Cancer and dental history: bone metastases diagnosed on April 2010; preventive tooth extraction (at other institution) on August 2010 and early start of monthly zoledronic acid on September 2010 (3 weeks later); reported incomplete socket closure; left mandible pain since January 2011; X-ray film was silent and a diagnosis of periodontal disease was made (at the same institution); pain decreased after oral antibiotic therapy. At our office observation time (August 2011), a little mucosal break (5 mm) with bone exposure was present. We retrospectively reviewed the routine bone scan (Tc99 scintigraphy) performed on April 2011, in comparison with previous exam: a new large mandible uptake had appeared (Fig. 1), whereas known bone metastases uptakes were reduced (after effective endocrine therapy). On September 2011, a new bone scan revealed a reduction of mandible uptake extension (Fig. 2) and a CT scan showed ONJ lesion not only in left mandible area but also in medial right mandible area (Figg.3-5). The mucosal break disappeared after conservative treatment (oral antibiotic; chlorhexidine mouth rinses). In the following 2.5 years, no other bone exposure area appeared, but two further episodes of pain (always on left mandible) occurred (resolved by antibiotics). Latest bone scans showed persistence of (reduced) left mandible uptake. **Take home messages.** 1. Male breast cancer are at ONJ risk, as well as female. 2 Avoid early BP start after tooth avulsion and use proper extraction protocols (1). 3. Please take attention to jaw area on routine bone scan: a new jaw uptake is suspect for ONJ. 4. CT scan is useful even in patients with apparently not severe clinical history and it is mandatory to stage ONJ.

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Category 2 B

Bevacizumab - related osteonecrosis of jaw in a rectal cancer patient never treated with bisphosphonates

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Osteonecrosis of Jaw (ONJ) has been reported not only after Bisphosphonate (BP) treatment, but also in patients receiving antiangiogenic agents (e.g., bevacizumab and sunitinib), alone or combined with BPs. Since the first description of ONJ associated with BPs for metastatic bone disease (2003), few ONJ cases in colorectal cancer patients have been described. We report a case of ONJ seen in a colorectal cancer patient after bevacizumab therapy and never treated with any BP.

Case report. On August 2011, we saw at our Oncology Unit a 60 year old man, complaining left mandible pain (VAS score 6) with a lingual side bone exposure, 1 cm diameter. He was under therapy with chemotherapy associated to bevacizumab. Cancer history: Rectal cancer and lung metastases diagnosis on February 2010; chemo-radiotherapy treatment and then rectal surgery; chemotherapy since August 2010; pulmonary metastases excision on November 2010; chemotherapy (FOLFIRI scheme) and bevacizumab between December 2010 and March 2011; due to pulmonary progression of disease, treatment within experimental drug protocol (other centre); diagnosis of brain metastases and radiotherapy on July 2011; following start of new chemotherapy (FOLFOX scheme) with bevacizumab again. Dental history: he was submitted to left mandible molar extraction on January 2011 (under bevacizumab treatment) and he had complained incomplete socket closure. On August 2011, at our first observation, we prescribed antibiotics and chlorhexidine mouth rinses, with pain reduction. CT scan showed bone mandible cortical lesion in previous tooth extraction.

Discussion. A tooth extraction during antiangiogenic therapy is a possible trigger of ONJ, even in patients not receiving BPs. Careful history has to be collected by dental specialists in cancer patients before oral surgery. If patients undergoing antiangiogenic treatment (bevacizumab, sunitinib, etc) without BPs should undergo preventive dentistry measures before starting treatment (as well as it is recommended for patients receiving BPs) has to be explored.

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Category 2 B

Role of nurses in a multidisciplinary team for prevention , diagnosis , treatment and follow-up of osteonecrosis of jaw (ONJ)

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The occurrence of ONJ is a serious event, with negative consequences on the QoL of cancer patients; biphosphonates are of great clinical benefit, but it is mandatory to monitor carefully their use in order to prevent the occurrence of ONJ.
On November 2005, at Alessandria Hospital, an ONJ Multidisciplinary Team for the prevention, the diagnosis and the treatment of ONJ was established; within the team, nurses are active as case-managers. At February 2014, we followed 496 patients (471 our hospital patients and 25 referred by other hospitals for consultation or second-opinion).
The case manager nurse becomes the figure of coordination of diagnosis path, treatment and care, as well as a reference for the patient and the whole multidisciplinary team. The nurse, since taking charge of the patient, is responsible for : booking of the first dental visit and control visits, booking of X-rays of the jaws or other diagnostic tests, monitoring the procedure followed from each patient, liaising contacts between different specialists and updating of clinical documentation. Of fundamental importance for the prevention is the nurse role of information and education on behavioral factors for an adequate and proper oral hygiene and the risk factors for the onset of ONJ. Managing and monitoring the clinical care pathway, the nurse is also involved in data collection and processing.
In conclusion, the nurse is a member of the Multidisciplinary Group, playing multiple roles: case manager when taking charge of a patient, when following and supporting him/her during adequate course of investigations, diagnosis and treatment; coordinator of the procedures to be implemented, indicated by several medical specialists; health educator implementing proper health interventions. Other nursing activities takes place on the front of the data management and participation in study protocols, hence outlining the role of the research nurse.

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Category 2 B

Description of a new protocol with application of PRP in post-extraction sockets of a patient treated with aminobisphosphonate

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Background. Platelet-rich plasma (PRP), an autologous product rich of growth factors, is an adjunctive bio-material able to promote healing in dental surgery, especially in elderly. It is also used for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ) and for application in post-extraction alveolar site in order to obtain mucosa healing and reduce BRONJ risk.
Aim. to describe a dental extraction PRP enriched protocol adopted in a patient treated with aminobisphosphonate in order to evaluate the healing of the post-extraction alveolar site.
Case report. An osteoporotic woman (71 yrs), treated with alendronate per os for 10 years and suspended from 1 year, currently with vitamin D and calcium, needed extractions of 3.1 – 4.1 since fractured. After hematologic screening, PRP

was prepared. Systemic antibiotics (ampicillin/sulbactam 500 mg/die by i.m. + metronidazole 1 g/die per os) and topical antiseptic (chlorexidine 0.20% rinse) have been administered, from one day before and seven days after extractionsontrol.
The teeth extraction were performed, by means of hand tools and local anesthetic without vasoconstrictor; after, intra-alveolar application of PRP and rifamicine were inserted and, lastly, in order to to close filling alveolus and to promote first intention healing, a surgical flap was carried out. At T1 (7 days before) suture was removed and a sub-total mucosal healing was observed; at T2 (30 days after), a complete clinical *restitutio ad integrum* was recorded and no BRONJ radiological sign was detected.
Conclusion. This is a simple surgical protocol, characterized by absence of any intraoperative difficulty for the operator and safety for patient, without any adverse effects due to use of an autologous bio-material. Although with limitation of the short follow up and a single case report, the protocol could be tested on a larger number of patients in order to evaluate the onset of BRONJ.

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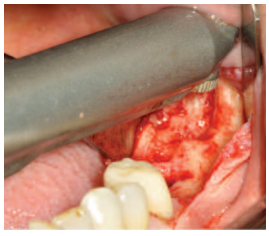
Category 2 B

Er:YAG laser surgery for treatment osteonecrosis of the jaw due biphoshonates (BRONJ): A predictable technique



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Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a serious oral complication resulting from oral or intravenous bisphosphonates. The patient (56 years old, female) reported in this paper developed BRONJ after treatment with zoledronic acid for multiple myeloma.BRONJ stage II was determined on the basis of clinical (suppuration, pain and inflammation of the surrounding soft tissues) and radiographic evaluations. A medical and surgical approach was applied. Once a week, the necrotic area was cleansed, in the hospital with sterile saline solution and was disinfectedwith 0,8% hydroxide hydrogen gel. Additionally, the patientwas instructed to disinfect and medicate the area at home 3 times a day after meals with gauze soaked in sterile saline of NaCl 0.9% and every 24 h with 0,8% hydroxide hydrogen gel. Both treatments were continued until complete healing was observed.Surgical managementincluded perioperative antibiotic therapy (amoxicillin clavulanate1 gr every 12 h and metronidazole 250 mg every 8 h) combined with a proton pump inhibitor (omeprazole 20 mg every 24 hours) for 7 days before and 7 days after the surgery. Surgery was performed under local anesthesia (mepivacaine 2% with adrenalin 1:100.000); a mucoperiosteal flap was realized and the lesion was evidenced;Er:YAG laser surgery was performed under continuous irrigation using the following parameters: continuous mode; wavelength, 2490 nm; energy, 250 mJ; frequency, 20 Hz; and power, 5 W. Patientwas evaluated with clinical follow-up examinations at 1, 2, 3, 6, and 12 months and radigraphic examination at 6 and 12 months.In this report, complete healing occurred after 1 laser therapy session demonstrating the effectiveness of this approach. The minimally invasive property and photothermal, photochemical, photoablative, photophysical, and photomechanical effects of laser surgery performed with the Er:YAG laser seem to have a good predictability as demonstrated in the international literature.

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Category 2 B

Osteonecrosis of jaw (ONJ): sometimes a life-threatening event. Literature review and two cases

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Background. Osteonecrosis of Jaw (ONJ) after Bisphosphonate (BP) treatment has large variability as clinical history and outcome. Even if a negative impact on Quality of Life has been described and demonstrated, ONJ is usually described as an event with mild or moderate sereneness. However, as a form of osteomyelitis with potential severe complications, ONJ can rarely be life-threatening. **Material and Methods.** We reviewed the ONJ literature (PubMed and other sources) looking for severe complications and/or lethal or life-threatening ONJ cases. We also reviewed history of 44 ONJ cases observed by our hospital ONJ multidisciplinary team. Results. We analyzed 36 papers potentially referring to severe cases of ONJ history (not related to surgery complications), not only in cancer patients receiving iv BPs but also in patients with osteoporosis and non-malignant diseases receiving oral BPs (Mehanna 2010, Ebker 2013). In our experience, 2 cases out of 44 (4.5%) had history of hospital admission due to severe infections related to ONJ. Case 1. A male patient, 65 years old, affected by Renal Cell Cancer and bone metastases, was admitted at the Intensive Unit of another hospital due to large neck infection with cellulitis. History revealed he had been treated with zoledronic acid and sunitinib. CT scan showed large mandible lesions compatible with an undiagnosed ONJ. The patient responded to antibiotic therapy and was homed some weeks. In the following 2 years, he showed ONJ in 3 quadrants. Case 2. A female breast cancer patient, 80 years old, was submitted on 2005 to several teeth extractions, after 5.5 years of monthly IV pamidronate treatment. She developed mandible skin fistulae and received numerous courses of antibiotic therapy; in one case she needed hospitalization to receive large spectrum IV antibiotics and blood transfusions. **Discussion.** Some ONJ patients (immunocompromised; treated with antiangiogenic agents; with comorbidity; elderly) can be at risk of life-threatening events correlated to ONJ.

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Category 2 B

Osteonecrosis of jaw (ONJ) in italy: 2014 update of role of italian patients, physicians, dentists, researchers

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Background. Osteonecrosis of jaw (ONJ) is an uncommon but severe complication observed mostly in patients treated with bisphosphonates (BPs) for bone metastases, myeloma, osteoporosis and firstly recognized on 2003. The number of cases observed in Italy appears high in comparison with other countries. On an online journal we have already published a review (1) about several aspects of ONJ in Italy and the role of Italian physicians and dentists on accumulating knowledge and ONJ reporting.: at October 2011, among 1272 papers published worldwide on ONJ issue, 128 (10%) were from Italian Authors. Relevant articles by Italian groups were published about pathogen-

esis hypotheses, animal models, biology studies, risk factors, preventive measures, dental extraction protocols in BP-exposed patients, laser therapy, ozone therapy, surgical treatment.

Material and methods. A manual searching was performed using a full text electronic journal database (Pub Med); the main applied key was "Osteonecrosis AND (jaw OR jaws)" , and publications including Italian authors were selected. Papers published between November 2011 and February 2014 were registered.

Results. We analyzed 585 further articles published worldwide on ONJ issue; 10.2 % of them (60) were from Italian Authors. We classified the latter items as follows: 25 (41%) are case reports and clinical experiences; 22 (36%) report a therapeutic or behaviour protocol; 3 (5%) were literature reviews; 9 (15%) were about surgical therapy; 1 (1.6%) was on base science.

Conclusions. We confirm that experience of Italian patients suffering from ONJ, together with work of Italian dentists, physicians and researchers, appears of paramount importance in order to study ONJ and minimize a possible severe side-effect of efficacious medical treatments.

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Category 2 B

Low doses of zoledronate stimulate in vitro human keratinocytes proliferation and migration

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Bisphosphonates (BPs) are widely used to treat a great variety of clinical conditions involving altered calcium metabolism. These drugs are characterized by a P-C-P structure which can be modified changing the two lateral chains on the carbon atom deeply influencing their biological and toxicological profile. Starting from 1970s, nitrogen containing BPs (N-BPs) entered in the oncological clinical practice to treat and prevent skeletal complications of multiple myeloma or bone metastases arising from different cancer types [1]. N-BPs therapy also shown well known side effects, including soft tissue and mucosal cellular toxicity [2].

In the present study zoledronate (Zol) has been used in an in vitro wound healing model to evaluate, the effect of low concentration (10 nM - 10 μM) of this N-BPs on human spontaneously immortalized keratinocytes (HaCaT) cellular behavior.

Surprisingly, at the tested concentrations, Zol stimulated keratinocytes proliferation, upregulating cytokeratin 5 while downregulating filaggrin expression. Moreover, Zol was also able to increase HaCaT wound healing ability, without any significant effect on MMP-9 activity. The lack of Zol effect on MMP-9 activity indicates that wound closure, in this experimental model, is mainly due to an increase in cell proliferation rather than to an increase in cell migration. [3]. It is known that Zol lowers farnesyl pyrophosphate (FPP) endogenous levels and that FPP could reduce both cell proliferation and migration by activating glucocorticoid receptors (GR). In this work it has been demonstated that Zol induced increase in HaCaT cell proliferation was due to a reduction in GR activation.

These results suggest new possible clinical applications for this compound in the field of epithelial regeneration.

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Category 2 B

Bisphosphonate related osteonecrosis of the jaws: case report in patient with multiple myeloma

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Background. Osteonecrosis of the jaw (ONJ) is a side effect of anti-resorptive therapy including bisphosphonate and denosumab. It Is defined as an area of exposed bone in maxillofacial region persisting for greater than 8 weeks with delayed healing in patients without prior history of radiation therapy to the jaws.
Case report. On October 2010 a 58-year-old man came to our attention for multiple myeloma with bone metastatis involved also mandible. The patient had chemotherapy and autologous stem cell transplantation. He was treated with zoledronic acid 4 mg IV every 4 weeks between 7 October 2010 to April 2012. On April 2012, therapy was discontinued due poor oral hygiene the patient was re-directed to dentist. On November 2013 he reported pain in right mandible. At oral examination, there was a bone exposure. Associated mucosa appeared inflamed and purulent exudate was present. Histopathological biopsy sample revealed necrotic osteitis and infiltrate of lymphocytes and granulocytes. A panoramic radiograph showed deep bony defect in right mandible. We instructed the patient to use chlorhexidine rinses and started therapy with antibiotic and oral antimycotic. In following three weeks, pain diminished almost completely, but conservative therapy failed to resolve the exposure. The surgeon recommended the patient to have surgical intervention to resect right mandibular body, but he refused.
Discussion. Identification of patients at high risk for ONJ is important to prevent this condition. Myeloma treatments (including bisphosphonate) are implicated in ONJ. There is increasing evidence that avoidance of surgical trauma and infection to the jawbones can minimize the risk of ONJ, but there are still a significant number of individuals who develop ONJ in the absence of these risk factors. Patients at higher risk for ONJ should be seen at short follow-up intervals after bisphosphonates treatment end.

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Category 2 B

Osteonecrosis of the jaw after long-term oral bisphosphonates, followed by short-term denosumab treatment for osteoporosis: a case report

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Of note, she also reported a previous incisor extraction that was performed in July 2012 (before denosumab) without ONJ onset.
Bisphosphonates and denosumab are antiresoptive agents and are mainly used for management of metastatic bone cancer, osteoporosis and other diseases. Bisphosphonates (BP) can reduce skeletal related events (SRE) by 30-50% [1]; denosumab (D) has been found even more effective than BP [2]. BP and D have been both associated to osteonecrosis of the jaw (ONJ).
We report a case of an osteoporotic woman (62yrs), complaining maxillary intense pain after a recent tooth molar ex-

traction, observed in July 2013 at our centre. She mentioned previous treatments with monthly ibandronate (Bonviva ® 150 mg) per os (from January 2003 to April 2010), risedronate (35 mg weekly, from May 2010 to May 2012) and two administrations (in August 2012 and in January 2013) of denosumab (Prolia ®, 60 mg sc every 6 months).
No further systemic or local risk factors were referred. Intraorally, bone exposure of right emimaxilla was present (see Figure); osteolysis area was observed in in CT scans. According to Bedogni et al. [3], the ONJ case was classified as stage II B. Medical therapy (ampicillin/sulbactam im 2 times/die, metronidazole per os 3 times/die, chlorhexidine 0.2% mouth rinses) was administered. One week later, the patient was asymptomatic but within the same stage (IIA); she was referred to Oral and Maxillofacial surgery for surgical management.

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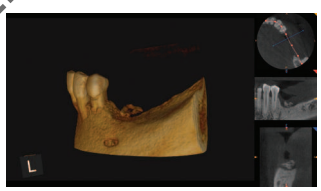
Category 2 B

Cone beam computed tomography vs. traditional CT in the diagnosis of osteonecrosis of the jaw: report of five cases



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Objective. The purpose of these cases is to demonstrate the advantages of an alternative approach for the early detection of Osteonecrosis of the Jaws. The authors compared the images provided by Cone Beam Computed Tomography (CBCT) with conventional OPT and CT Dentascan, showing the best results of CBCT in diagnosis of disease onset.
Materials and methods. We examined patients with manifestation or suspicion of ONJ involving upper and/or lower jaw; all were affected with bone metastasis (from breast, bladder or prostatic cancer) and were treated with biphosphonates. They were subjected to clinical and instrumental examination; images provided by OPT and traditional CT Dentascan were compared with the ones got by CBCT (CS 9000 3D; Carestream Health Inc.).
Results and conclusions. Quality of CBCT images show a clear superiority compared to the traditional OPT and CT Dentascan images. Two dimension images or three dimension reconstructions at high resolution allow the identification of pathological bone alterations where other examinations were negative or uncertain. For this reason the CBCT can be used as an alternative to traditional CT in patients with diagnosed or suspected ONJ. High resolution CBCT restricts the examination to a limited bone area with the risk of not detecting other ONJ lesions, given that in 10-20% of cases osteonecrosis occurs in multifocal form.
Another significant advantage of this technique is the lower amount of radiation provided to the patient: the CBCT supplies radiation doses from 3 to 8 times lower compared to traditional CT for the same irradiated volume.
We, therefore, hope for performing CBCT, following a clinical examination and an OPT, in order to identify the clinical signs of the disease in the early stages of its development,
However 5 cases are not sufficient to establish, with absolute certainty, the superiority of CBCT images compared to conventional examinations and further works are needed.

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Category 3

Oral health management of patients under i.v. bisphosphonate treatment

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Background. Patients treated with Bisohosphonates and other antiresorptive agents (denosumab) are at risk of Osteonecrosis of Jaw (ONJ). Oral health management is fundamental both in primary prevention (to avoid ONJ onset) and in secondary prevention (after ONJ onset, to avoid complications and relapses/multifocality).
Patients and Methods. In our department, the management of patients under IV Bisphosphonate treatment follows two different protocols based on presence or absence of osteonecrosis injury.
Group 1 (no ONJ group): the hygiene check-ups are important to verify the compliance of the patient, given the needed motivation, and to monitor the presence of possible events, such as infections (bacteria or mycosis) , mucositis, mucosal lesions due to prosthetic decubitus, early bones exposures, pain.
Group 2 (ONJ cases and patients submitted to extractions or oral surgery): the oral hygiene is very important, because it helps to control infection and pain, and it is essential during the preparation of the surgery; the wound healing will be easier and the secondary infection will be less common.
Results 2013. Group 1 (371 patients): In these patients dental management is: First visit with OPT Rx in order to make dental extracions of compromised teeth before the beginning of the treatment. Lesson of oral hygiene. Follow-up during drug treatment. Oral surgery just in case of unfixable teeth (in according to our hospital protocol.
Group 2 (91 patients who had surgery with piezosurgery device): 15 ONJ cases and 76 minor oral surgery. Short-term visits for oral health control.
Conclusions. The oral prevention can reduce ONJ occurrence in patients under Bisphsphonate therapy.
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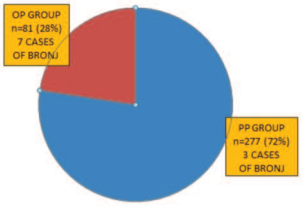
Category 3

Osteonecrosis of the jaws in cancer patients with bone metastasis: a preliminary analysis of a single center prevention experience



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Introduction. Osteonecrosis of the jaws is a complication that can occur in patients treated with bisphosphonates (BPs)[1]. This complication is frequent and severe in patients with neoplastic diseases involving bone[2].
Patients and methods. The objective is to evaluate the effectiveness of a program of dental prevention in patients undergoing treatment with BPS .
In this study 377 patients (median age 66 years, 207 female, 170 males) were referred to our unit from January 2007 to November 2011. All the patients were due to be treated with zoledronic acid (ZA) and no one have ever received head and neck radiotherapy. No signs or symptoms of osteonecrosis of the jaw were detectable in the clinical exami-

nation. No BPS therapy was previously given to 277 (72%) patients (prevention group PP), while 81 (28%) patients (observation group OP) had already received a mean of 6.3 infusions of ZA at the time of enrolment. The PP group underwent oral surgery (326 teeth/roots were removed) in order to eliminate dental risk factors before starting BPS therapy; the OP group received only conservative dental treatments. All the patients presented for a regular follow-up.
Results. The PP group received a mean of 8 doses of ZA (mean follow-up: 472 days); the OP group 5 doses of ZA (mean follow-up: 508 days).
In total there were 10 cases of BRONJ: 3 in the PP group (1% prevalence) and 7 in the OP group (8.6% prevalence). The statistical analysis (χ^2 test) was significant ($p<0.001$). The trigger event was the need for surgical dental procedures (2 cases in the PP group and 7 in the OP group). 1 case in the PP group showed bone exposure without identifiable cause but after implementation of cancer therapy with anti-angiogenic drugs.
Discussions. Take preventive dental measures reduces the risk of bisphosphonate related osteonecrosis in an onco-haematological population candidate for treatment with ZA[3], even if is not possible to completely elucidate the risk of developing this complication.
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Category 3

Validation of a risk reduction protocol for dental extractionin patients at risk for jaw osteonecrosis: a retrospective cohort study

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Aim. The aim of this study wasto evaluate the incidence of bisphosphonate-related jaw osteonecrosis (BRONJ) after implementation of an established risk reduction protocol.
Patients and methods. A retrospective cohort study was performed. Patients exposed to nitrogen-containing bisphosphonates (N-BPs) and admitted for the extraction of compromised teeth at the Universities of Verona and Padova between April 2008 and March 2013were recruited for the study. Inclusion criteria were a) metastatic bone disease or multiple myeloma treated with i.v. N-BPs and non-malignant bone disease treated with oral N-BPs for at least 3 years; b) lack of clinical/radiologic signs of BRONJ in the jaw where dental extraction was required and c) exposure to a defined treatment protocol consisting ofsurgical tooth extraction, alveolar bone biopsy and tension-free mucosal flap closure.[1] Only patients who regularly attended the 3, 6 and 12-month clinical/radiological follow-up were included. Primary outcome was the 1-year incidence of BRONJ, defined as the occurrence of clinical and radiological signs of disease.[2]Alveolar bone histology was tested as predictor of BRONJ.
RESULTS. 178 patients were eligible for the study; of whom 97 fulfilled all required criteria and were included. They were mostly females (73,7%), with a median age of 65 years. Osteoporosis was the most frequent diagnosis followed by multiple myeloma and breast cancer; zoledronate was the most common N-BP prescription (45,5%). The estimated 1-year absolute risk of BRONJ in the study population was 0.03. Osteomyelitis/osteonecrosis was found histologically in two patients, who developed clinical/radiologic signs of BRONJ within the study period. In addition, one patient with normal bone at histology developed BRONJ.
CONCLUSION. The surgical tooth extraction protocol described by Saia et al minimizes the risk of BRONJ. Despite the limited number of events, baseline osteomyelitis/osteonecrosis at histology is a confirmed predictor of BRONJ development.
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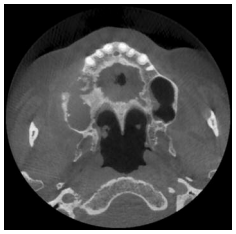
Category 3

Bronj prevention: 9 years of clinical practice



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Bisphosphonates are drugs largely used in bone-involving pathologies, such as solid tumor, osteoporosis and multiple myeloma. The main oral side effect is an increased risk of developingosteonecrosis of the jaws. Follow-up of patients treated with bisphosphonates is a key factor in order to reduce this occurence.
731 patients have been followed since 2004: 473 of them had an out patient clinical evaluation before starting bisphosphonates therapy; 235 came to our attention for the first time when they had already started drug administration, and 23 came to our observation with a suspect of ONJ which was confirmed. Out of these 731 patients, 347 had solid tumors, 241 multiple myeloma, 103 osteoporosis. The remaining patients were suffering of arthrosis, rheumatic polimyalgia, multiple sclerosis or other systemic pathologies.
Our protocol consists of a first clinical examination followed by clinical reevaluation every 3 to 6 months: for patients who are planned to start BP therapy we allow to start treatment only after all necessary dental procedures had been performed (tooth extractions or infection removal); for patients who are already under treatment we provide a 3 to 6 months follow up control and when dental surgery is necessary, the BP therapy is temporarily interrupted.ONJ developed in 34 of our patients: 16 of them affected by solid tumors, 13 by MM, 3 by osteoporosis and 1 by rheumatoid arthritis. The treatment schedules were: intravenous Zoledronate once a month (22 cases), iv Pamidronate once a month (6 cases), oral Aledronate once a week (4 cases), oral Risedronato once a week (1 case) and imClodronate (1 case). Twenty-three patients had the diagnosis confirmed at our first evaluation; the remaining 11 developed it during follow-up. This stated a prevalence of 1.5% in our patients' cohort.
We can underline the importance of prevention and follow-up in BP-treated patients in order to detect and remove all possible risk factors for ONJ and make early diagnosis.

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Category 3

Tooth extractions in intravenous bisphosphonate-treated patients: the CIR-Dental School experience

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Purpose. Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is a complication in a subset of patients receiving drugs used to treat malignant bone metastases. Numerous studies have identified potential risk factors associated with its development, above all a history of dentoalveolar trauma, long duration of drug exposure and the intravenous use of potent bisphosphonate (e.g. zoledronic acid). To date, dentoalveolar trauma is the most common risk factor. The aim of this prospective hospital-based study was to describe the experience of two different surgical protocols for tooth extractions in patients with a history of intravenous use of zoledronic acid.
Patients and methods. Patients were collected at the Oral Surgery Unit of *CIR-Dental School* in Turin. Prospective subjects with a follow-up of at least 12 months were included. Surgical procedure, using an ultrasonic surgical appa-

ratus (Mectron Piezosurgery DeviceÒ) and autologous plasma rich in growth factors (PRGF), was undertaken. The only difference between the two protocols was the use (GROUP A) or not (GROUP B) of a flap technique.
Results. One hundred and sixty-five patients participated in the study. Five hundred and ninety tooth extractions were performed. Differences between surgery sessions were analysed and the surgical time proved shorter for the patients treated without flaps (P<.05); furthermore, this group had fewest post-extraction complications (P<.05). A failure rate of 2.7% (A) and 1.4% (B) was reported.
Conclusions. To date, few protocols have been suggested to decrease the development of BRONJ. Most existing publications have proposed that dental treatment should be conservative; above all, extraction and all types of surgical interventions involving bone exposure should be avoided. The proposed surgical protocols appear to be a good choice of treatment; the use of PRGF and piezosurgery brought positive results. The protocol without the vestibular flap appears to be faster and simpler.

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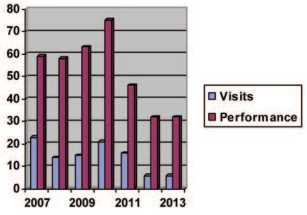
Category 3

Prevention of ONJ in patients with bone metastases treated with bisphosphonates: Oncology and Odontostomatology clinical experience



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Introduction. Bisphosphonates (BP) are potent inhibitors of bone resorption used mainly in the treatment of metastatic bone disease. Even though patient's benefit of BP therapy is wide, various side effects may develop. Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is among the most serious ones. Actually, the only defense is the onset prevention, assessing and eliminating local risk factors.
Material and methods. Oncology Unit with Dentistry Department of general Surgery, Martini Hospital, Turin, since 2007, have sampled 101 patients screened before BP therapy. The patients are sent to the Dentistry Unit, where they are visited, to assess the presence of apical periodontitis, incongruous prosthetic denture and to be motivated and educated in proper oral hygiene during subsequent therapy with BP. In edentoulus patients, the removable denture was examinated and prepared if not congruous for the anatomical features of the patient. In precence of periapical lesions, the interested teeth were extracted and the patients was subject to professional oral hygiene, root scaling and bony courettage, where indicated. After three months, Oncology Unit proceeded with the administration of BP; the patients were checked by dentistry during BP therapy.
Results. To date, 101 patients were observed (365 performances). All patients underwent treatment with BP up to a maximum of 24 doses. We found no case of osteonecrosis, at the moment. All the patients were examinated for a period of follow up of 12 months after the end of therapy: during this period no bisphosphonate- related complications were observed.
Conclusions. Prevention has lead to a progressive reduction in the prevalence of BRONJ. Any patient for whom prolonged bisphosphonate therapy is indicated should be provided with preventive dental care. In our experience, conservative management and periodic follow-up were sufficient to minimize the risk of developing this severe condition.

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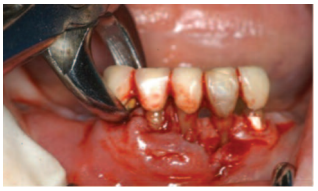
Category 3
Esperienze di prevenzione (pre-trattamento con BP) e/o follow-up

Tooth extractions in high risk patients for bisphosphonates related osteonecrosis of the jaws



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Introduction. Trauma during dental surgery is a known predisposing factor for bisphosphonates related osteonecrosis of the jaws (BRONJ).
Here we report our experience of tooth extractions in patients at high risk because of previous BRONJ.
Materials and methods. Eighty-two tooth extractions were performed in 36 patients (12 males, 24 females) at the Center of Oral Surgery and Oral Pathology of the University of Parma, Italy.
Forty-nine tooth extractions were performed in 21 patients (3 males, 18 females) who were previously treated and completely healed for BRONJ in a site different from that of extraction (Group 1 – G1). Thirty-nine of these extractions were performed in 14 cancer patients (6 multiple myeloma; 8 bone metastases) and 10 tooth extractions in 7 osteoporotic patients. Twenty-three tooth extraction were performed in mandible and 26 in maxilla.
Thirty-three tooth extractions were performed in 15 patients (9 males, 6 females) who had BRONJ in the same site of extraction (Group 2 – G2). All these extraction were performed in cancer patients (5 multiple myeloma; 10 bone metastases). Twenty-eight tooth extractions were performed in mandible and 5 in maxilla.
In all patients were administered post-extractive sessions of Low Level Laser Therapy (LLLT) through Nd:YAG laser (power 1.25 W; frequency 15 Hz – fibre diameter 320 µm; 5 application of 1 minute each). Antibiotic treatment was administered from three days before extraction to mucosal closure of the socket.
Mean follow-up was 18.66 months in G1 (ranging from 3 to 44), 13.93 months in G2 (ranging from 3 to 22).
Results. In a total of 82 tooth extractions, post-extractive BRONJ was observed in 2 cases (incidence: 2.44%) that completely healed after surgical treatment (follow-up from post-extractive BRONJ: 33 months).
Conclusion. Protocol we used for tooth extractions has been effective for reducing the incidence for post-extractive BRONJ also in high risk patients already treated for jaw osteonecrosis.

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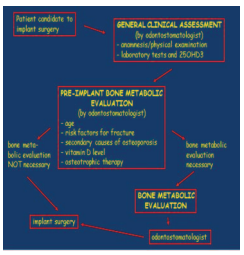
Category 3

Pre-implant osteometabolic screening (SOMI): an interdisciplinary collaboration between medicine and odontostomatology



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Today odontostomatologists increasingly have to consider middle-aged and elderly patients afflicted with osteoporosis for implant surgery. These patients are often receiving osteotrophic therapy and are usually prescribed bisphosphonates. Because of the bone exposure during oral surgery and the well known association between bisphosphonate therapy and implant failure due to jaw osteonecrosis (ONJ), well documented in literature, an osteo-metabolic pre-implant evaluation by a specialist in mineral metabolism and bone disorders (rheumatologist, endocrinologist, internist, orthopedic or geriatric), allows, in certain cases, the patient to undergo implant surgery in best clinical and pharmacological condition, optimizing the quality of surgery and reducing the implant failure risk to a minimum.
The goal of this work is to give dentists a rapid and effective tool (SOMI) that can identify which patients undergoing implant surgery require a preliminary bone metabolism evaluation.

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Category 3
Prevention experiences

Osteonecrosis of jaw (ONJ) in prostate cancer patients: report of a monoinstitutional experience

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Background. Bone is the most frequent site of metastases from prostate cancer, both of endocrine sensitive disease and of castration-resistent disease. Skeletal Related Events (SRE) due to bone metastatic lesions increase morbidity. The treatment is based on endocrine therapy, chemotherapy, radiotherapy ; the therapy scenario is changing due recently introduced new agents (abiraterone acetate, enzalutamide, vaccines, etc). Bone metastatic prostate cancer patients are often treated with antiresorptive agents, such as Bisphosphonates (BPs), including Pamidronate, Zoledronic Acid, Ibandronate, or an anti-RANKL agent, Denosumab. All these agents are associated with adverse events, including Osteonecrosis of Jaw (ONJ) that can occur in 0-18 % of prostate cancer pts. Preventive (risk reduction) measures before BP and Denosumab treatment (dental visit, dental RX, eventual teeth extractions, dental care, denture fitting) have been recommended.
Materials and methods. We reviewed all prostate cancer patients affected by bone metastases observed by our team at the Oncology Unit in years 2005-2013. They were classified as: a) Hystoric group (patients already under BP treatment on 2005); b) Prevention group (patients undergoing preventive measures before BP therapy start); c) Screening group (patients treated with BPs, not receiving prevention due to several reasons, on years 2006-2013).
Results. We followed 56 pts treated with BPs and/or Denosumab. ONJ was observed in 4/56 pts (7.1%). In the Historic group we observed ONJ in 1 out of 3 pts, and in the Screening group in 1 out of 5 pts (globally: 2/8, 25%); in the Prevention group in 2 out of 48 patients (4.1%). Further 5 ONJ cases in prostate cancer patients were referred to our Multidisciplinary Team by other neighbour hospitals (all not receiving preventive visit).
Conclusions. Prostate cancer patients are at high risk of ONJ. The preventive measures can minimize the rate of ONJ and are recommended.

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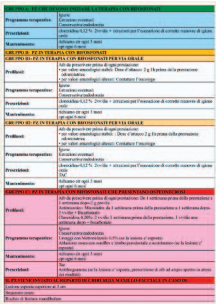
Category 3
Poster 3

Bisphosphonates and BRONJ: actualization of protocols for patient prevention and assistance



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Introduction. Numerous episodes of jaw osteonecrosis, because of surgical therapies in patients treated with bisphosphonates, have led to investigate the possible causes and associated risk factors. Thus, in 2005, was born the "Project Bisphosphonates team", Department of Conservative and Endodontics , directed by Prof. Luca Bartorelli, which receives patients directly from oncology wards as well as from other departments or other colleagues. The aim of this study is to monitor patients already taking this class of drugs and patients that will take them.
Materials and methods. The team, in order to standardize data collection, has developed a first tab which is reserved to the signaling centers, in which is described the pathology of origin, the pharmacological treatment, type, duration, dosage and mode of subministration. A second card is the dental record, which also collects instrumental examinations. The patient is so brought back to one of three study groups: the first (Group A) patients that must begin a cycle of bisphosphonates, the second (Group B) patients already treated but free of necrotic lesions, and the third (Group C) patients with BRONJ.
Discussion. In the 9 years of activity, the team has visited more than 300 patients, divided according to sex, primary disease, the way of subministration of bisphosphonates , the duration of treatment: separate protocols were applied in relation to the study group (all data are shown in the tables).
Conclusions. The "Project Bisphosphonates team" since 2005, acts in two directions: to provide a model of prevention and assistance to patients taking bisphosphonates and contribute to increase the information around these diseases.The proposed protocols are strictly connected to the guidelines recently published by SIPMO in 2014, and hence it derives a further validation for the activity carried out to date and encourages its continuation.

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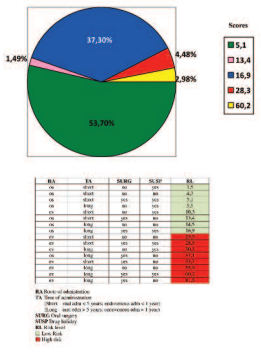
Category 3

Oral surgery in patients assuming bisphosphonates: a statistically based RISK index of developing BRONJ after oral surgical procedures



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Objective. The objective of the present study is to elaborate and to verify a statistically-based index that can be used by clinicians to assess the risk level of BRONJ in patients assuming these drugs.
Materials and Methods. One hundred-sixteen patients on bisphosphonate therapy were enrolled and grouped based on Woo's classification. Data regarding selected risk factors were collected and analyzed using multivariate logistic regression to show their relation to BRONJ. In addition the multivariate logistic regression formula was developed to realize an index of the risk level of BRONJ. The data were presented with a 10^2 correction.
In a second step of the study 67 patients which required surgery, were enrolled to verify this index. For each patient was calculated a score of the risk based on the selected variables. All the surgeries were performed under antibiotic therapy. Follow up was scheduled at one week, one, three, six twelve months to the surgery.
Results Multivariate logistic regression analysis resulted in values of statistical significance for the variables "route of administration", "time of administration", "suspension" and "oral surgery".
The values resulting from the multivariate logistic regression formula were presented in **Table 1**. The scores were grouped into two risk classes: high and low. The scores calculated for the surgically treated patients were presented in **Figure 1** .
The surgeries performed were 167 dental extractions, 10 dental implant insertions, 1 sinus augmentation procedure and 1 enucleation of a cystic lesion. The wound healing occurred in all cases but not in 1 patient with a score of 60.2 who developed BRONJ that healed in 3 months of conservative management. Two patients with a score of 28.5 showed a delayed healing.
Conclusion On the base of our sample this index seems to be able to predict the risk of developing BRONJ after oral surgical procedures; indeed the low rate of BRONJ development is due to the fact that the 92,54% of surgeries were performed in patients with a score lower than 25,5 (value fixed as cut-off between the low and high risk). However a larger sample of patients will be required for the full validation of this risk index.
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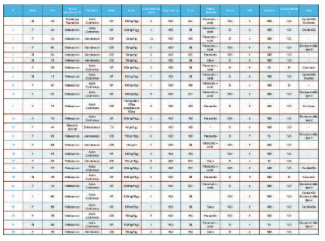
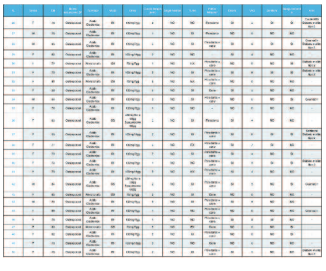
Category 3

Effect of lower level laser therapy after to othextraction in patients under bisphosphonate therapy





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Introduction. The diode laser isused in the Lower Level Laser Therapy (LLLT) (1, 2). It stimulates the bone formation and repair. Some cellular chromophorer eceptors, like endogenous porphyrins or cytocrome c-oxidase, transforms the light into metabolic energy with an increase of mRNA for collagen type I/III synthesis. The aim of this work is to evaluate the clinical efficacy of LLLT for the prevention of Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ), considering different clinical values.
Methods. Fifty patients in therapy with bisphosphonate under went too thextraction and were randomized, under antibiotics prophylaxis,: group A (25 patients) was treated with laser in the alveolus (1.2 W, 10 Hz, 30 seconds) and oxygen water; in group B (25 patients) laser was not used (control group). A questionnaire about pain, swelling, postop bleeding was administered to both groups.

Results. The results are shown in the picture.
Conclusions. It's not possible to demonstrate the effectiveness of the LLLT in the prevention of BRONJ at the moment, but LLLT appears to be promising in reducing the post-op pain and in obtaining a better control of hemostasis with out effect on swelling.

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Category 3

Decreased occurrence of ONJ after preventive measures: the Alessandria experience on a 471 bisphosphonate patient population

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Background. Osteonecrosis of Jaw (ONJ) cases were firstly diagnosed and recognized in our Hospital on 2005. Since 2006, a ONJ Multidisciplinary Team was established (including maxillofacial surgeons/dentists, oncologists, hematologists, nurses, radiologists, nuclear medicine and infective disease specialists, data managers). Preventive (risk reduction) measures before Bisphosphonate (BP) treatment (dental visit, dental Rx, eventual tooth extractions, dental and denture care) have been planned, according to early recommendations and their modifications (1-3).
Material & Methods. We reviewed all the patients observed by our Team and treated at the Oncology-Hematology Department in years 2005-2013. They were classified as : a) "historic group" (patients already under BP treatment on 2005); b) "prevention group" (patients undergoing preventive measures before BP therapy start); c) "screening group" (patients treated with BP, not receiving prevention due to several reasons, on years 2006-2013); d) "no therapy group" (pts undergoing preventive visit but that never or not yet started BP therapy).
Results. We observed 471 pts; 410 received BP: M/F 166/244; median age 68 years (range 32-87); 168 breast cancer / 117 myeloma / 56 prostate cancer / 30 lung cancer / 11 renal cancer / 28 others; 174 zoledronic acid, 142 pamidronate, 29 ibandronate, 65 combination of BPs (52 pamidronate-zoledronic acid); median BP duration 13 months (range 1-119). The ONJ rate was 5.85% (24 out of 410), but with a clear-cut difference between groups, on the base of receiving or not preventive measures : 11.6% (10/86) in the historic group, 12.7% (7/55) in the screening group, 2.6% (7/269) in the prevention group.
Conclusions. Our 8-year experience appears as confirming the positive effect of preventive (risk reduction) measures before and during BP therapy.

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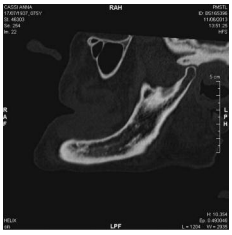
Category 3

C-Terminal Cross-Linking Telopeptide Test in course of Bisphosphonate-Associated Osteonecrosis of the Jaws



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An adverse effect of bisphosphonate therapy (BP) is BP-related osteonecrosis of the jaw (BRONJ)[1]. The C-terminal cross-linking telopeptide of type I collagen (CTX) assay is a serologic test to predict the risk of BRONJ, but at present no obvious consensus on its effectiveness has been reached[2]. This report describes a case of BRONJ of the jaw with evaluation of CTX in the phases of the BRONJ clinical manifestation. A 77-year-old woman was admitted to our Department in October 2012, complaining of swelling sensation in the region of left mandibular. Her medical history revealed that since 2006, she had been taking 2.5 mg of methotrexate six times a week and 70 mg of Fosamax® (alendronate sodium) once a week for the treatment of rheumatoid arthritis. Besides, she also reported steroids use during eighteen years. The patient had no history of radiotherapy, infectious process or trauma in the maxillofacial region. Clinical examination revealed an ulceration of the alveolar mucosa associated with bone exposure, without painful symptoms and purulent discharge (Fig.1). Radiographic analysis showed bone loss associated with osteosclerosis. Bone scintigraphy revealed increased radioisotope uptake in the left mandibular area. Serum CTX test was solicited to evaluate the bone reabsorption status, which revealed values of 32 pg/mL. Mouth-rinsing with chlorhexidine 0.20% was prescribed and, after medical consensus, alendronate suspension was recommended. The patient underwent to pre-operative hyperbaric oxygen (HBO) therapy for 20 sessions, antibiotic therapy (Clavulin three times a day), sequestrectomy, bone debridement and again post-operative HBO therapy for 10 sessions. CTX test was performed 5 months after surgical treatment and revealed normal values (245 pg/mL).Although the drug interruption can lead a gradual improvement in the values of CTX test[3], our report indicates that CTX values reflect the metabolic healing status of the bone jaw.

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Category 3

Periodontal status of a population with high Risk for Bisphosphonate- Related Osteonecrosis of the Jaw (BRONJ) development

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Background. Bisphosphonates (BPs) are drugs for bone diseases suchas multiple myeloma and osteoporosis, preventing skeletal disability and prolong survival. Patients frequently suffer of BP side effects that negatively impact on the quality of life, such as Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) (1). BRONJ onset and progression is due to BPs and many local risk factors, such as periodontal conditions. Marx et al. noted that 84% of BRONJ patients had periodontal disease, including 29% with advanced disease (1). Prevention of BP side effects

and BRONJ onset and progression is a challenge for medical team (2). AIM. To evaluate the association between periodontal disease and BRONJ development risk and the effect of periodontal treatment on BRONJ risk. **Methods.** All study subjects were enrolled from Dental Clinic, S. Anna Hospital, Ferrara: 123 BP-treated or candidate to BP-treatment patients were eligible for this study. Each patient was asked for general and dental anamnestic data, comorbidities and history concerning BPs. All patients underwent a comprehensive oral examination and clinical parameters were recorded. **Results.** Clinical data from all patients were included at baseline, though some data were missing because of edentulism obtained after multiple extractions. All participants had received or were going to receive intra venous zoledronate, oralal edronate, or both. Effectivness of periodontal treatment was assessed comparing records at baseline and after 6 months. In un adjusted analyses, baseline and 6 months data diddiffer in terms of average Probing Depth (PD), Bleeding On Probing (BOP), or percentage PD> 4 mm. However, the data didn't differ significantly for average Plaque Index (PII). **Conclusions.** Although several studies, including Thumbigere-Math et al. (3), did not find an association between recorded periodontal parameters and BRONJ onset, some evidence suggest that oral infections affect BRONJ risk

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Category 3

Role of dental prevention of bisphosphonates-related osteonecrosis of the jaws: 5 years longitudinal study in cancer patients

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In the present study all patients that from 2004 to 2013 have made at least one administration of zoledronic acid at the Oncology Unit of the Hospital of Parma for bone metastases from solid tumors were examined to assess the occurrence of BRONJ after a specific preventive dental program performed at the Oral Medicine and Pathology of Laser-Surgery Unit.

For each patient, it was decided to record the medical history, drug therapies, as well as all the oral factors that could be related to the onset of BRONJ, such as the presence and type of prosthetic rehabilitation, periodontal status and previous extractions.

The 156 analyzed patients were divided into two groups according to the realization or not of a dental evaluation before the bisphosphonates therapy: Group 1 of 60 patients who were evaluated during or after bisphosphonate therapy and Group 2 of 96 patients who received a dental preventive evaluation before bisphosphonates therapy. Two hundred thirteen patients were excluded from the analysis because they did not received any oral evaluation.

The statistical analysis showed that Group 1 and Group 2 differ significantly ($p = 0.019$) with regard to the incidence of BRONJ (G1: 18,3% - G2: 6.3%), with the most number of events in Group 1, and a tendency to develop BRONJ after 2 years 3 times greater in Group 1 than in Group 2.

In order to assess the role of other factors in the development of BRONJ, it was applied a binary logistic regression and multivariate analysis. The only values that reached significance by multivariate analysis have been severe periodontal disease ($p = 0.025$) and having carried out extractions ($p < 0.01$).

This 5 years longitudinal study highlighted as the dental prevention is a fundamental factor in reducing, but not completely eliminating, the onset of BRONJ, and as other factors, in particular the presence of severe periodontal disease and the extractions, contribute in the development of BRONJ.

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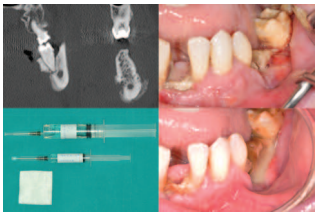
Category 4

Peroxide hydrogen gel. An antiseptic therapy for ostenonecrosis of the jaw due to biphosphonates



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Antiseptic therapy to manage osteonecrosis of the jaw due to bisphosphonates has been widely described in literature. Different types and formulations of oral antiseptics such a 0,12%, 0,2% or 1% Clorexidine (CHX) and a 0,8% or 3% Hydrogen Peroxide (H_2O_2) have been proposed to treat BRONJ superinfections. As reported in many literature's studies, CHX is known to cause inhibitory effects in human oral fibroblasts and cell death occurring within minutes for human gingival fibroblasts exposed to 0.2 and 2 mg/ml. On the contrary, the use of H_2O_2, only at high concentration, has been linked to many different oral complications and adverse effects. Many studies, however, have shown that no carcinogenic activity or adverse effects could be observed after a lengthy exposure to 3% ,or less, H_2O_2. Because of this, we have decided to introduce the regular use of 0,8% H_2O_2 in gel formulation to disinfect BRONJ lesion. Gel formulation, due to its characteristics, can decrease oral mucosa toxicity and increase efficacy over BRONJ lesion, in comparison with oral rinse. In this study, 18 BRONJ patients (4 stage 1; 11 stage 2; 3 stage 3) have been included in a strict antiseptic program. We divided BRONJ in plane or crater-like lesions. In hospital, 11 plane ostheonecrosis have been weekly cleaned using a gauze simply soaked in 0.9% NaCl solution and they have been accurately disinfected with 0,8% H_2O_2 gel. Additionally, these patients have been told to medicate BRONJ at home, 3 times a day after meals with gauze soaked in 0.9% NaCl solution and every 24 h with 0,8% H_2O_2 gel. On the other hand, as usual in hospital, 7 crater-like osteonecrosis, instead of just being cleaned with gauze soaked they have been weekly irrigated with 0,9% NaCl , as well as been disinfected with 0,8% H_2O_2 gel. BRONJ have been irrigated at home 3 times a day after meals with 0,9% NaCl solution; every 24 h 0,8% H_2O_2 gel has been applied. No patients have reported any adverse effect using 0,8% H_2O_2 gel.

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Category 4

Role of Piezosurgery in prevention of Osteonecrosis of Jaw (ONJ) in patients under bisphosphonate therapy

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Background. Bisphosphonate-related Osteonecrosis of Jaw (BRONJ) is a serious medical complication that may affect patients in treatment with bisphosphonates for bone metastasis, multiple myeloma and long term oral treatment for osteoporosis. For these patients, tooth extractions are thought to be the main trigger of ONJ. Teeth extractions with Piezoelectric alveolar curettage could guarantee a higher chance of quick healing.

Materials and Methods. On 2013, 38 patients under therapy with IV Bisphosphonates (BPs) for cancer treatment were submitted to dental extraction (43 procedures), as well as 36 patients (46 procedures) in treatment with BPs (oral and not). The following surgical technique was adopted : local anaesthesia, dental extraction, Piezoelectric alveolar curettage, incision and lifting of the half thickness edge for covering of the extracting site and conseguent healing of primary intention, stressless suture with Vicryl in detached stiches. The pharmacological therapy was : amoxicillin + clavulanic acid, 1g twice a day for 21-30 days beginning 3 days before the oral surgery (or as an alternative treatment: claritromicina 500mg twice a day); mouth rinses with chlorhexidine 0.2%; antalgic therapy if needed.
Results. Patients in treatment with IV zoledronate (4 mg every 28 days): we performed 57 dental extractions (on 43 procedures). Out of 57, 55 sites healed: 51 of primary intention and 4 after a surgical revision of post-extractive wound. Two patients did not heal and needed secondary oral surgery.
Patients in treatment for osteoporosis received several types of bisphosphonates : oral alendronate 15, oral risedronate 12,oral ibandronate 3, IV Aclasta (zoledronate) 3, IM clodronate (up to over 20 years) 3.We performed 61 dental extractions (46 procedures): healing sites 61 (100%).
Conclusion. Piezosurgery tecnique is useful for safe extractions, as well as for ONJ treatment.

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Category 4

Severity of incident cases of osteonecrosis of jaw (onj) in one year experience

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Background. Could severity of ONJ depend on diagnosis time, during follow-up (after preventive measures) versus observation diagnosis (in patients not submitted to preventive visits)? Could Piezosurgery be beneficial in both patient groups?
Material and Methods. We reviewed the incident ONJ cases in one year (2013) in our department, looking for patient characteristics and treatment outcome.
Results. On 2013 we have checked 371 patients (243 at Candiolo Cancer Center and 128 at our Hospital Department). We observed 14 new ONJ cases : 11 under treatment with IV bisphosphonates and 3 under treatment with oral bisphosphonates. Out of 14 cases, 6 were in the “prevention group” (patients in follow-up and receiving preventive visits before and during treatment) and 8 in the “no follow-up group” (observed in patients not seen before).
SICMO – SIPMO grading
Prevention (6): stage 1b 1; stage 2 4; stage 3 1
No follow-up (8): stage 1a 1; stage 1b 1; stage 2a 1; stage 2b 2; stage 3 3
Main trigger
Prevention (6): extractions 4; prosthetic decubitus 2
No Follow-up (8): extraction 2; periodontal disease 3; prosthetic decubitus 3
Surgery outcome (12-18 months after resection with Piezosurgery):
Prevention (6): 6 healings
No Follow-up (8): needed larger surgery due to delayed diagnosis. Outcome: 7 healings, 1 no surgery according to patient’s decision.
Conclusions. ONJ in patients not submitted to preventive visits is generally more severe but can benefit from surgery (with piezosurgery technique) in the same way.

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Category 4

Bisphosphonate-related osteonecrosis of jaw in patients with osteoporosis: surgery outcome

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Since 2009 to late 2013 we observed 17 cases of jaw osteonecrosis in patients under treatment with bisphosphonates for osteoporosis. All cases came to our observation with evident disease.
Out of 17 cases, 14 had resection surgery with Piezoelectric device (following our hospital protocol) and 3 had no surgery : one for dexitus, ad two for general patient conditions incompatible with narcosis.
Among the 14 cases submitted to surgery, we collected the following data:
Average Age: 78 years
Bisphosphonate treatment: Alendronate 10 / Risendronate 3 / Ibandronate 4
Median duration of treatment: more than 4 years
Concomitant therapies : cortisone 4-- methotrexate 3.
Concomitant disease: rheumathoid arthritis 2, diabetes with insuline therapy 2, chronic lymphatic leukemia 1
ONJ sites: 12 mandible, 5 maxillary
Main trigger: tooth extraction 11; periodontal disease 5; prosthetic decubitus 1.
SICMO – SIPMO grading: Stage 1a 2 ; Stage 2a 1 ; Stage 2b 10 ; Stage 3 4 .
All cases are in follow-up and at the moment no patient shows ONJ relapse.

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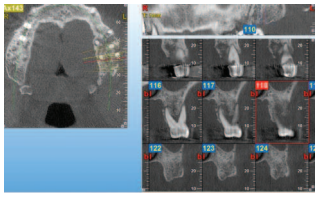
Category 4
Esperienze di trattamento di ONJ (≥10 CASI)

Use of cone beam computed tomography for surgical planning in bisphosphonates-related osteonecrosis of the jaws. a review of clinical cases.



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Introduction. One of the problems in treatment of bisphosphonate- associated osteonecrosis of the jaws (BRONJ) is to understand which radiological imaging technique allows to assess the extent of BRONJ. Cone beam computed tomography (CBCT) is an attractive modality for 3-dimensional imaging of the jaws, for its ability to characterize the nature and the extent of radiographic changes, across different stages.The purpose of this study is to investigate the efficacy of CBCT in the surgical planning of BRONJ. There are a lot of studies in literature about the role of CBCT in diagnosisiter of BRONJ; these studies underline the importance of CBCT to confirm the diagnosis of BRONJ but few

studies investigate the role of CBCT for planning the surgical treatment.
Material and methods. We observed 40 cases of BRONJ in patients affected by oncological diseases and osteometabolicdesorders, between 2011 and 2014. For 16 patients we required CBCT; for 24 patients we required OPT exam.
The surgical treatments were: debridment, marginal bone resection or segmental bone resection. We based on clinical and radiological findings to choose the most appropriate surgical treatment in every single patient. We observed an high correlation between the anatomic location of BRONJ during surgical treatment and CBCT radiological findings. On the other hand, OPT exam couldn't produce same results compared to CBCT.
Conclusion. In our experience, we can assert that CBCT is a useful and effective tool in the surgical planning of BRONJ. It gives a lot of informations about the extension of osteonecrosis and about cancellous and cortical bone quality envolved. The CBCT also allows to show complications such as oro-sinusal, oro-nasal or mucocutanea fistulas and their 3-D tracts, pathological fractures, maxillarisosteolysis, sinusitis, cheekbone and palate osteosceloris.This study about CBCT in BRONJ treatment is in according to SIPMO 2013 recommendations.

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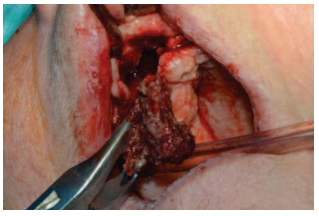
Category 4
Esperienze di trattamento di ONJ

Surgical outcome of patient affected by stage III of BRONJ: a preliminary report



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Aim. Aim of this study was to evaluate the outcomes of surgical treatment in patient affected by stage III bisphosphonate-related osteonecrosis of the jaw (BRONJ).
Materials. A prospective study was designed to assess the surgical management in patient affected by Stage III of BRONJ. Twenty patients, were surgically treated, with conservative surgical technique, and followed for at least 6 months. The primary outcome variable was a change in BRONJ staging (improvement, worsening, or no change). Age, gender, underlying disease, tabagism, comorbidity were also analysed.
Clinical data. Twenty subjects (15 women; 75%; average age, 69,8 yr; standard deviation 12,8 yr; age range 36 to 86 yr) were selected. The underlying diagnoses included breast cancer in 7, multiple myeloma in 6, prostate cancer in 4, and osteoporosis in 3. The bisphosphonates(BPs) used were zoledronate (18 subjects, 90%) and alendronate. Thirty-five percent of the lesions were located in the mandible (7 subjects). All the BRONJ lesions were symptomatic. An oral-antral communication was detected in 13 cases, a pathologic fracture in 1 and extra-oral fistula in 6 cases. The main event leading to BRONJ was extraction (13 subjects, 65%).
Effect of surgical treatment. Sixty-eight per cent of subjects showed improvement after surgery. Among the unsuccessful ones (7 subjects), two were successfully treated with segmentai mandibulectomy and microvascular free flap reconstruction (MFFR).
Conclusion. *The majority of the subjects showed significant improvement with conservative surgical technique. In case of unsuccessful outcome, major resective interventions may be considered.*

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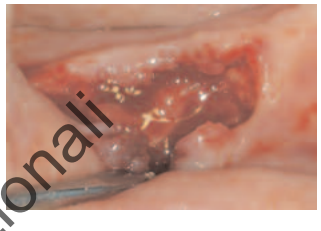
Category 4

The combination of laser-assisted surgery with prp for the treatment of bronj in cancer patienta. a pilot study



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Aim. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a well-known potential complication of bisphosphonates (BPs) therapy and its treatment could reckon on different approaches. Recently, encouraging results for BRONJ were showed from some clinical studies using Er, Cr: YSGG laser-assisted surgery. Platelet-Rich Plasma (PRP), a new approach to promote tissue regeneration and healing, may be a promising complementary therapy. The aim of this pilot study is to study the effectiveness, in terms of clinical healing, of a combined treatment (laser-assisted surgery and topical PRP) for BRONJ in a group of cancer patients.
Methods. Ten oncological patients (3 males, 7 females), aged 69-89 years, mean age 76.2±5.8) with BRONJ were consecutively recruited. BRONJ was classified (T_0) according to [1]. All patients underwent pre- and peri-operatory antibiotic prophylaxis, and preparation of autologous PRP; the following combined surgical protocol was applied: i) exposure of the surgical area, through the creation of surgical edges; ii) courettage of the necrotic bone and, if present, sequestrectomy, by using a Er, Cr: YSGG laser; iii) application of autologous PRP over the entire bone cavity; iii-ii) suture of surgical flaps. All patients performed a CT after 3 months from surgery (T_1) in order to re-stage of the disease. Successfultreatmentswereconsideredthe complete healing and the radiologicalimprovement (transition from a higher stage to a lower one).
Results. At T_0 6/10 patients were stage IB, 2/10 were stage IIA and 2/10 were stage IIB. At T_1, 3/10 (30%) cases (2 cases IB and 1 case IIB) showed no clinical and radiological signs of BRONJ relapse; 5/10 (50%) cases (4 cases IB and 1 case IIB) showed clinical improvement, whereas 2/10 (20%) (both IIA) showed no-improvement.
Conclusion. The association oflaser-assisted surgery and topical PRP, firstly investigated in this study, seems useful in BRONJ healing among cancer patients. Further investigation is necessary in order to validate these preliminary results.

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Category 4

Medical, surgical and laser-assisted management of 247 patients affected by Bisphosphonates-Related Osteonecrosis of the Jaw (BRONJ)s: ten years experience

E. Merigo E, M. Meleti, I. Giovannacci, C. Fornaini, P. Vescovi

Objective. To compare medical, surgical and laser-assisted approaches for the treatment of BRONJ.
Methods: Two hundred and forty-seven patients (70 males, 177 females; 187 oncological and 60 non oncological patients) affected by BRONJ were evaluated at the University of Parma, Italy, between 2004 and 2014. Sites were subclassified as follows: Group 1 (G1): 33 sites treated with medical therapy; Group 2 (G2): 51 sites treated with medical therapy associated to Low Level Laser Therapy (LLLT); Group 3 (G3): 17 sites treated with the combination of medical and surgical therapy; Group 4 (G4): 43 sites treated with the combination of medical and traditional surgical therapy with LLLT; Group 5 (G5): 69 sites treated with the combination of medical and laser-assisted surgical therapy. Outcome of treatment was assessed using the staging system proposed by Ruggiero: transition from a higher Stage to a lower one for at least 6 months was considered as clinical improvement and suggestive of a successful treatment.
Results. Clinical improvement was achieved in 8 out of 33 (24.2%) BRONJ sites in G1. Sites of G2 with an improvement were 36 out of 51 (70.6%). Eleven out 17 BRONJ sites (64.7%) in G3 had a transition to a lower stage after treatment. A clinical improvement was recorded in 39 out of 43 cases (90.7%) in G4 and in 61 out of 62 cases (97.1%) in G5. Complete healing was obtained in 65 out of 69 cases (94.2%) in G5.
Conclusions. In our experience, percentage of success obtained with a combined approach based on medical, surgical (including laser-assisted) and LLLT (G4-G5) is significantly higher than percentage of improvement obtained in G1, G2 and G3.
Relevance. The management of BRONJ is still controversial: the introduction in the treatment protocols of laser-assisted and surgical approach could improve the therapeutic results.

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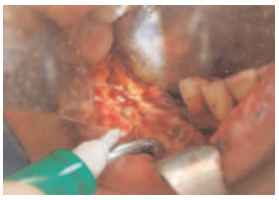
Category 4

Surgical treatment protocol of bisphosphonate-related osteonecrosis of the jaws (BRONJ): long-term follow-up of 266 lesions



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Aim. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is the most serious side effect in patients receiving bisphosphonates (BPs) for cancer disease and osteoporosis. The aim of this study is to evaluate the success rate of

our surgical treatment protocol of BRONJ lesions after a long-term follow-up.
Methods. From 2004 to 2013, 145 neoplastic and 58 osteoporotic patients with 266 BRONJ lesions referred to the Odontostomatology Unit of University of Bari. The treatment protocol consisted of OPT and CT evaluation, suspension of BPs therapy after multidisciplinary medical consultation not less than 3 months before surgical procedure, administration of 3 cycles of ceftriaxone and metronidazole, and surgical debridement in minor lesions or marginal resection in major ones. Surgery was complemented by piezosurgery of the residual resection margins, and with the intra-cavitary application of a gel compound made of hyaluronic acid and amino acids (gly, leu, lys, pro) to obtain a faster healing of both hard and soft tissues, without infective complications thanks to the wound mechanical protection. All the samples were histologically examined, and patients could restart BP therapy after the complete soft tissues healing, at least 1 month after surgery.
Results. The protocol we propose for the management of BRONJ showed optimum results during the follow-up period, which was not less than 12 months in all patients and more than 30 months in the 80% of osteoporotic patients; 226 lesions healed (84.47%), whereas 34 lesions recurred (12.64%): 30 lesions among neoplastic patients (15.39%) and 4 lesions among osteoporotic ones (5.63%). Five patients with six lesions succumbed for complications related to their cancer disease and chemotherapy.
Conclusions. This protocol could be a successful management strategy for BRONJ, considering the low recurrences rate and the good stabilization of the surgical sites observed after a long-term follow up.
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Category 4

A rational approach to the surgical treatment of bisphosphonate-related osteonecrosis of the jaw

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Background. In the BisphosphonateRelatedOsteonecrosis of the Jaw (BRONJ) thereis a reduction of the osteoclasticactivity, of the bone turnover and of the vascularization (avascularosteonecrosis). Regarding the treatment of BRONJ a lot of guidelines are published (1,2, 3). The aim of this work is to improve the surgicalaspect of the guidelines by experiencearriving from over 100 treatedcases.
Methods. The diagnosisisbased on clinical and instrumentalexams, likepanoramicradiography and CT, scintigraphy and MR. So The patients areclassified in 3groups: 1- patientsstartingbisphosphonate treatment 2- patients in therapywithoutsymptom of pain 3- patients in therapy with symptoms of pain or osteonecrosis.
Results. In groups 1 and 2 prophylacticsurgery and antibiotic or antisepticstherapy are needed. In group3hyperbaricoxygentherapy (HBO) and osseousresection are needed.
Conclusions. In group 3 patients the free flap reconstruction or metal plates were often a failure (a case in the picture) and they were rejected. The necrosis of bone transplanted in BRONJ patientsis more frequent than in cancer patients. There is also the risk of osteonecrosis in the area where the reconstructions crews are inserted. In our opinion the reasons for this is the poor vascularity and angiogenic capacity, which is typical of this region, and the accumulation of bisphosphonate in the other parts of the skeletonused for free flap. Only respective surgery is recommended.
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