EU/IT Multicenter Studies (ON/OFF) and the "DoctOral" System for ONJ

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The aim of the presentation is to describe two new technological projects applied in the field of medicine and pathology of the oral cavity.
On Off (Osteonecrosis Oral Findings & Future), supported by AIFA national project "Farmaci anti - angiogenetici e rischio di osteonecrosi dei mascellari - progetto multicentrico su dati retrospettivi, ottimizzazione della farmacovigilanza e della prevenzione secondaria, studi genetici", is a web portal, aimed for the collection of medical history, clinical and radiological findings related to patients with drug-related osteonecrosis of the jaw. The coordinating and validating center of cases is represented by the Sector of Oral Medicine "V. Margiotta" in Palermo, and all data may be carried out following recognition of credentials in different national centers that will join free of charge. The creation of this information system will break down the power bias resulting from imprecise set of data on this new and serious emerging disease, in order to have more control in the incidence value and to give a fast service of second opinion for management. Primary goal is to widen our network, in order to design multicentric study and confirm the need of a standardization of the diagnostic and therapeutic protocols.
Doctoral® is an application (currently free of charge), which will be accessible on iOS and Android platforms, and will provide, exclusively for healthcare professionals and students of the School of Medicine, a tool for achieving the diagnosis of oral lesions: it is a matter of an easy pattern way, by means of questions and answers, to find the possible diagnosis. In addition, everyone, at the end, can take advantage of the second opinion service by mail.
These projects are under the patronage of SIPMO.

Effect of prevention on the incidence of BRONJ: three years clinical follow-up

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Background. Bisphosphonates (BPs) are unstable equivalents of pyrophosphate that bind selectively to bone and are supposed to act selectively on osteoclasts during high bone turnover, resulting in an anti-resorptive effect[1]. BPs are indicated in the treatment of bone metastases, especially in breast and prostate cancers, as well as in multiple myeloma, osteoporosis, and malignant hypercalcaemia, where these agents produce a significant reduction in skeletal complications, such as pathological fractures and spinal cord compression. Despite the high efficacy of BPs in the treatment of several diseases, some side effects have been reported, including osteonecrosis of the jaws[2]. In 2003, Marx reported the first cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ), and since then, many other cases have been reported. BRONJ has been clearly defined as a clinical scenario characterized by three diagnostic features: (1) current or previous treatment with a BP; (2) the presence, for longer than 8 weeks, of exposed bone in the maxillofacial region; and (3) no history of radiation therapy to the jaws[3]. The aetiology of BRONJ remains unknown. The multifactorial pathogenesis is related to many local and/or general factors, including disruption of the normal bone turnover cycle, compromised angiogenesis, inhibition of oral cell wound healing, genetic polymorphisms and microbial biofilm. Several recent studies have focused on the risk factors for developing BRONJ. In the recent position paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS), BRONJ risk factors are categorized as drug-related, local, demographic and systemic, or genetic.

Among cancer patients exposed to zolendronate, the cumulative incidence of BRONJ is in the low single digits (range = 0.7 - 6.7%). When limited to studies with Level 1 evidence, i.e. systematic reviews or RCTs, the risk of BRONJ in subjects exposed to zolendronate approximates 1% (100 cases per 10,000 patients)[4,5]. The risk of ONJ among cancer patients exposed to zolendronate ranges between 50-100 times higher than cancer patients treated with placebo.

The implementation of dental screening and appropriate dental measures before initiating antiresorptive therapy reduced the risk of ONJ in several prospective studies when compared in a retrospective fashion to patients who did not undergo dental preventive measures.

Dimopoulos[6] found a statistically significant, almost threefold reduction in the incidence of osteonecrosis in patients when preventive measures were applied. Bonacina[7] did not report any new cases of ONJ in patients who received dental screening and necessary dental treatment before initiating IV bisphosphonate treatment. Vandone[8] found the incidence rate of developing ONJ was reduced by 50% in patients who were screened and received preventive dental care before initiating drug therapy.

Materials and method. From 1 January 2009 to December 2011, all patients candidate to BPs therapy (zoledronate) were referred to the Department of Dentistry and Oral Surgery of the University Hospital of Pisa in order to search and eliminate all oral ONJ risk factors and to correct dental conditions that were thought to negatively influence oral health during BP therapy. At the first visit, all patients underwent a clinical oral examination and radiological assessment using orthopantomography (OPT). All potential ONJ risk factor (hopeless teeth, periodontal disease, peri-implant disease, inadequate endodontic treatments) were evaluated and corrected.

At the end of this first preliminary examination, if patients were diagnosed as free to the previous conditions, they were considered eligible for future therapy. If this was not the case, patients were accordingly treated and planes for a second preliminary visit. Zoledronic acid was administered at 4 mg over 15 min every 4 weeks.

Results. Eight hundred ninety-two subjects (611 women, 68%; average age 64.2 yr; standard deviation, 11.3 yr) were identified and included in the present study. All subjects included were previously scheduled to intravenous BP treatment with zoledronic acid for malignant diseases such as metastatic breast cancer (467 patients, 52%); metastatic prostate cancer (143 patients, 16%); multiple myeloma (104 patients, 12%); lung cancer (70 patients, 8%). Only 60,1% of the sample was considered eligible to begin zoledronic therapy. At three years follow-up no BRONJ cases were detected.

Conclusion. Our data suggests that preventive measure adopted in our protocol contributed to eliminate the risk of BRONJ new cases during three years follow up period.

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Dental extractions in rats treated with zoledronate and dexamethasone: histomorphometric and western blot analysis of osteopontin and osteocalcin

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Introduction. Among risk factors of Medication-related Osteonecrosis of the Jaws (MRONJ), dento-alveolar surgery, and in particular dental extractions, are by far the most important. Indeed a rate ranging from 52 to 61% of patients with MRONJ reported a tooth extraction as the precipitating event[1]. Different Authors had proposed several surgical protocols to manage tooth extractions in at risk patients. All these protocols share antibiotic therapy and differ for some surgical procedures (such as the removal of the alveolar bone all around the socket and the creation of tension free mucoperiosteal flap for wound closure)[2] or for some adjuvant therapies (e.g. ozone or the use of platelet rich derivates)[3-5]. Some case series describing the positive outcome of these preventive strategies have been published, but to date there is not evidence of superiority of a protocol over the others.

The use of low level laser therapy (LLLT) gave promising results in the prevention of post-extractive MRONJ[6].

The aim of the study was to investigate the effect of LLLT on the post-extractive socket healing in rats treated with zoledronic acid and dexamethasone.

Material and methods. Thirty male Sprague-Dawley rats were divided in 4 groups: control group (C, n = 5), laser group (L, n = 5), treatment group (T, n = 10) and treatment plus laser group (T+L, n = 10). Rats of group T and T+L received zoledronate 0,1 mg/Kg and dexamethasone 1 mg/Kg every 2 days for 10 weeks. Rats of group C and L were infused with vehicle.

After 9 weeks the first maxillary molars were extracted in all rats. Rats of groups L and T+L received laser therapy (Nd:YAG, 1064 nm, 1.25W, 15Hz, 5 min, 14.37 J/cm^2) in the socket area at days 0, 2, 4 and 6 after surgery. At 8 days from extraction, the sockets were clinically assessed with a grading score and the wound area was measured with a dedicate software (Image J 1.48v). The maxilla of each rat was then split in two parts: the right side was submitted to histomorphometric evaluation and the left side was processed to perform a western blot analysis. Antibodies anti-osteopontin (1:1000, Abcam, Boston, MA, USA) and anti-osteocalcin (1:1000, Abcam, Boston, MA, USA) were used.

Results. Group T+L showed a trend toward a better clinical grading score compared to group T (grade I 22% *vs* 28% - grade II 56% *vs* 28% - grade III 22% *vs* 44%, respectively). The average wound area was similar among the groups. Inhibition of osteoclastic alveolar bone resorption was found in groups T and T+L ($P<0.001$).

We observed that the expression levels of the cleaved and non-cleaved forms of OPN were not statistically different among the 4 groups ($P = 0.775$ and $P = 0.458$, respectively).

We found a significant difference between the four groups in terms of osteocalcin expression ($P = 0.0001$).

In particular, osteocalcin was more expressed in group L *vs* C (+ 348%, $P = 0.013$), and in group T+L *vs* T (+ 400%, $P = 0.002$). Moreover we observed that laser-dependent induction of osteocalcin was not prevented by zoledronate and dexamethasone treatment, since a significant difference was found when group T+L was compared with group C (+ 290%, $P = 0.025$) and when group L was compared with group T (+ 479%, $P = 0.002$). Osteocalcin expression was not influenced by pharmacological treatment, as shown by the comparison of groups T *vs* C ($P = 0.973$) and by the comparison of groups T+L *vs* L ($P = 0.813$).

Conclusion. Our findings suggest that laser irradiation after tooth extraction can promote osteoblast differentiation, as demonstrated by the higher expression of osteocalcin. Thus, laser irradiation could be considered a way to improve socket healing in conditions at risk for MRONJ development. Further researches are needed to better clarify the effects of lasertherapy on hard and soft tissues and to support the use of laser light in the prevention of post-extractive osteonecrosis.

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Workshop

A critical review of the literature on osteonecrosis of the jaw in patients treated with non-bisphosphonates drugs: prevalence, proposed mechanism and clinical features

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The growing number of osteonecrosis of the jaw associated with non-bisphosphonate drugs has induced in 2014 the American Association of Oral and Maxillofacial Surgeons (AAOMS) to introduced the new definition: "Medications-Related Osteonecrosis Of The Jaw (MRONJ)"[1]. The aim of this critical literature review is to show the findings from studies published on patients affect of MRONJ caused of non-bisphosphonates drugs. Current literature highlights several classes of drugs as RANKL inhibitors (denosumab), angiogenesis inhibitors (bevacizumab), VEGFR inhibitors (sunitinib, sorafenib, cabozantinib), mTOR inhibitors (everolimus, temsirolimus), selective estrogen receptor modulator (raloxifene) which can cause the osteonecrosis of the jaw with mechanisms of action different from bisphosphonates[2]. These drugs seem to interfere with the bone remodeling process i.e. alter to the balance between bone resorption and bone formation, or through the reduction of the angiogenesis, which could be the most plausible explanation for pathogenesis[2]. It has been recently suggested that an infective process could be the factor initiating the development of osteonecrosis of the jaw[3,4]. For some of these medications the scientific evidence is not as broad as for bisphosphonates and moreover in many patients with osteonecrosis of the jaw, above all associated with antiresorptive agents, remaining undiagnosed (absence of exposed necrotic bone and/or absence of sintomatology)[5].

Denosumab decreases bone turnover by inhibiting the binding of RANKL in the cell membrane of osteoclasts and osteoclast precursor cells[6] with complete suppression of osteoclastogenesis. This drug can linger in the body for a finite period of time by virtue of its low affinity to hydroxyapatite and the effects are expected to be short-lived and thus dissipate within 6 months of therapy cessation. Recent meta-analysis[7] noted that the overall rates of osteonecrosis of the jaw were significantly higher with denosumab as opposed to bisphosphonates. Due to the lack of solid evidence from clinical studies, the prevalence of osteonecrosis of the jaw among patients treated with denosumab for osteoporosis is difficult to assess.

Bevacizumab (anti-VEGF agents) inhibits angiogenesis or formation of new blood vessels. The incidence of ONJ with bevacizumab is about <1%[8]. Based on the available data, it seems plausible that bevacizumab use confers a relatively low risk for osteonecrosis of the jaw development. However, this risk could be amplified if bevacizumab is added to a background of bisphosphonate therapy in which case the osteonecrosis of the jaw risk becomes comparable to if not greater than that observed with bisphosphonates[2,9].

Sunitinib (treatment of metastatic renal carcinoma), sorafenib (metastatic hepatic carcinoma), cabozantinib (metastatic medullary thyroid cancer) have highlighted risk of osteonecrosis of the jaw approximates that of bevacizumab (0.2-0.4%)[10] .

Everolimus, temsirolimus are a relatively new class of therapies that are mainly used in the treatment of metastatic renal carcinoma and raloxifene commonly used for the prevention and the treatment of osteoporosis and breast cancer, at present there are only case reports.
A case of osteonecrosis of jaw with history of dengue infection (dengue fever is a common mosquito-borne disease prevalent in many countries including India) and chronic periodontitis is described in literature.
The real epidemiological burden remains still unclear and is practically impossible to make a list of the drugs responsible of the MRONJ, given that with a frequency almost daily are marketed medications for treatment and/or prevention of osteoporosis and anticancer drugs potentially capable of osteonecrosis. The literature highlights that majority of MRONJ cases caused of non-bisphosphonates drugs occurred in patients suffering from malignant diseases and osteoporosis. The most prevalent clinical feature was exposed necrotic bone in the oral cavity (mandible and in particular for molar and premolar regions in both jaws) which was accompanied by pain[11]. Among the characteristics and risk factors of patients affected of MRONJ as a consequence of the assumptions of non-bisphosphonate drugs it is essential analyzing that in their clinical history (co-morbidities and co-medications) have assumed bisphosphonate and non-bisphosphonate medications. The combination of any of these drugs along with radiation therapy could increase the risk of developing osteonecrosis of the jaw.
MRONJ remains a significant risk associated with the use in particular of bisphosphonates and RANKL inhibitors (denosumab) and a small percentage of other non- bisphosphonates drugs as a side effect of an anticancer therapy and treatment of osteoporosis. Therefore, as reported a recent study[12], the likelihood of developing MRONJ can be minimized through the implementation of prophylactic dental assessment and active dental intervention.

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Workshop

ONJ: is the scaremongering validated by clinical evidences?

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Introduction. ONJ is defined as the presence of necrotic bone in the oral cavity of a patient treated with bisphosphonate or targeted therapies with no history of radiation in the head and neck region. An accurate knowledge of the burden of effective prevention and management of oral complication associated with the administration of bisphospho-

nates is really necessary among the scientific community. To establish the impact of oral complications associated with such therapies, an exhaustive systematic review was completed on 2010 by volunteers from the Oral Care Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). Management recommendation and guideline classification was based on criteria of the American Society of Clinical Oncology rating the level of evidence and grade of recommendation for each considered variable.
Materials and methods. The aim of this review is to determine the prevalence of ONJ and its relationship with quality of life, economic impact, with the final aim to formulate evidenced based guidelines thus analysing the current publications of the literature.
Results. The mean weighted prevalence of ONJ for all reviewed studies is 6.1%, while 13.3% of them present documented follow-up while 0.7% had undocumented follow-up = 0.7%. Among all studies, 1.2% of them were represented by epidemiological studies. Concerning the management of ONJ the following strategies have been considered: the use of antibiotics (59.7%), a simple bone sequestrectomy (23.4%), the suspension of the prescribed drug (16.1%), a conservative therapy (15.2%), the execution of extensive surgical debridement (12.8%), unspecified surgery along with antibiotics prescription (6.8%) and the use of IV antibiotics with patient hospitalization (0.6%). The response to these therapies has been poorly reported with 47% of responses not clearly specified in published studies. BON completely resolved in only 12% of cases, while 33% remained stable and 7% progressed. Due to flaws in published studies and the paucity of data regarding management strategies, no guideline is possible regarding prevention or treatment strategies (level of evidence III, recommendation grade C).
Conclusion. Oral complications associated with the administration of bisphosphonates and/or target therapies are common and have a higher prevalence among cancer patients. This issue represents a crucial challenge for clinicians and the systematic review by the Oral Care Study Group of MASCC/ISOO provides a thorough assessment of the available literature for these oral complications. An up-to-date is now under elaboration by the Oral Care Study Group of MASCC/ISOO and these current results will be shortly published.

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Workshop

Targeted therapy in oncology: new drugs for everyone?

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Cancer is one of the leading causes of death in the United States and Europe along with heart disease. The hallmark of cancer treatment has been conventional chemotherapy. Chemotherapeutic drugs are designed to target not only rapidly dividing cells, such as cancer cells, but also certain normal cells, such as intestinal epithelium. Over the past several years, a new generation of cancer treatment has come to the forefront, i.e, targeted cancer therapies. Like conventional chemotherapy, targeted cancer therapies use pharmacological agents that inhibit growth, increase cell death and restrict the spread of cancer. As the name suggests, targeted therapies interfere with specific proteins involved in tumorigenesis. Rather than using broad base cancer treatments, focusing on specific molecular changes which are unique to a particular cancer, targeted cancer therapies may be more therapeutically beneficial for many cancer types, including lung, colorectal, breast, lymphoma and leukemia. Moreover, recent advances have made it possible to analyze and tailor treatments to an individual patient's tumor. There are three main types of targeted cancer therapies; 1) monoclonal antibodies, 2) small molecule inhibitors and 3) immunotoxins.