Alessandria 19-11-2011

Bifosfonati endovena nei pazienti oncologici ed ematologici: misure preventive pre BF

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PREVENZIONE PRIMARIA

Adozione di interventi e comportamenti in grado di evitare o ridurre l’insorgenza di una malattia o di un evento sfavorevoli

2011: NON COMPLETAMENTE

MEDICI

ODONTOIATRI

2011: DIS - INFORMAZIONE ??

PAZIENTI

UNITO

GENETICA

GENETICA

Dovrebbe essere in grado di dirci quale pz ha maggiori possibilità di sviluppare una BRONJ

ma..

Ad oggi ancora pochi sforzi in questa direzione: reports di dubbio valore scientifico e mediocre utilità

Blood. 2008 Oct 1;112(7):2709-12. Epub 2008 Jul 1.

Bisphosphonate-related osteonecrosis of the jaw is associated with polymorphisms of the cytochrome P450 CYP2C8 in multiple myeloma: a genome-wide single nucleotide polymorphism analysis.

Sarasquete ME, García-Sanz R, Marín L, Alcoceba M, Chillón MC, Balanzategui A, Santamaria C, Rosiñol L, de la Rubia J, Hernandez MT, Garcia-Navarro I, Lahuerta JJ, González M, San Miguel JF.

Department of Haematology, Molecular Biology, and Human Leukocyte Antigen (HLA) Unit, University Hospital of Salamanca, Spain.

Abstract

We have explored the potential role of genetics in the development of osteonecrosis of the jaw (ONJ) in multiple myeloma (MM) patients under bisphosphonate therapy. A genome-wide association study was performed using 500 568 single nucleotide polymorphisms (SNPs) in 2 series of homogeneously treated MM patients, one with ONJ (22 MM cases) and another without ONJ (65 matched MM controls). Four SNPs (rs1934951, rs1934980, rs1341162, and rs17110453) mapped within the cytochrome P450-2C gene (CYP2C8) showed a different distribution between cases and controls with statistically significant differences (P = 1.07 x 10(-6), P = 4.231 x 10(-6), P = 6.22 x 10(-6), and P = 2.15 x 10(-6), respectively). SNP rs1934951 was significantly associated with a higher risk of ONJ development even after Bonferroni correction (P corrected value = .02). Genotyping results displayed an overrepresentation of the T allele in cases compared with controls (48% vs 12%). Thus, individuals homozygous for the T allele had an increased likelihood of developing ONJ (odds ratio 12.75, 95% confidence interval 3.7-43.5).

PMID: 18594024 [PubMed - indexed for MEDLINE] **Free full text**

Primo studio genetico.
Genome wide: numeri troppo bassi x avere significatività statistica ?

Int J Oral Maxillofac Surg. 2011 Jun;40(6):605-11. Epub 2011 Mar 10.

Genetic polymorphisms and other risk factors associated with bisphosphonate induced osteonecrosis of the jaw.

Katz J, Gong Y, Salmasinia D, Hou W, Burkley B, Ferreira P, Casanova O, Langaee TY, Moreb JS.

Department of Oral Medicine, College of Dentistry, University of Florida, Gainesville, USA. jkatz@dental.ufl.edu

Abstract

Bisphosphonate induced osteonecrosis of the jaw (BONJ) is a complication in patients taking bisphosphonate (BP) that affects their quality of life and compliance. In this cohort study, patients with multiple myeloma (MM) on intravenous BP therapy were enrolled over 1 year. Demographic and clinical data and genotyping of 10 single nucleotide polymorphisms (SNPs) from seven candidate genes associated with drug or bone metabolism were determined. Of the 78 patients enrolled, 12 had BONJ. The median time to developing BONJ was 28 months. Univariate and multivariate analysis revealed a significant association between BONJ and smoking (p=0.048) and type of BP treatment (p=0.03). A trend for higher odds for BONJ was found for SNPs in five genes: COL1A1 (rs1800012), RANK (rs12458117), MMP2 (rs243865), OPG (rs2073618) and OPN (rs11730582). Considering all five SNPs together, patients with genotype scores ≥ 5 had a BONJ event rate of 57%; those with scores < 5 had a rate of 10%. The adjusted odds ratio was 11.2 (95% confidence interval of 1.8-69.9; p value 0.0097). Smoking, type of BP and combined genotype score of COL1A1, RANK, MMP2, OPG and OPN were significantly associated with BONJ in MM patients undergoing BP therapy.

PMID: 21396799 [PubMed - indexed for MEDLINE]

Campione piccolo (12 pz) e associazione con altri fattori di rischio: fumo, BF ecc..

Ther Clin Risk Manag. 2010 Nov 19;6:579-83.

A SNP in CYP2C8 is not associated with the development of bisphosphonate-related osteonecrosis of the jaw in men with castrate-resistant prostate cancer.

English BC, Baum CE, Adelberg DE, Sissung TM, Kluetz PG, Dahut WL, Price DK, Figg WD.

Molecular Pharmacology Section, National Cancer Institute, Bethesda, MD, USA.

Abstract

A single nucleotide polymorphism (SNP) in CYP2C8 (rs1934951), was previously identified in a genome-wide association study as a risk factor for the development of osteonecrosis of the jaw (ONJ) in patients receiving bisphosphonates (BPs) for multiple myeloma. To determine if the same SNP is also associated with the development of ONJ in men receiving BPs for bone metastases from prostate cancer, we genotyped 100 men with castrate-resistant prostate cancer treated with bisphosphonates for bone metastases, 17 of whom developed ONJ. Important clinical characteristics, including type and duration of bisphosphonate therapy, were consistent among those who developed ONJ and those who did not. We found no significant correlation between the variant allele and the development of ONJ (OR = 0.63, 95% CI: 0.165-2.42, P > 0.47). This intronic SNP in CYP2C8 (rs1934951) does not seem to be a risk factor for the development of bisphosphonate-related ONJ in men with prostate cancer. It is important to note that this is only the second study to investigate the genetics associated with BP-related ONJ and the first to do so in men with prostate cancer. More studies are needed to identify genetic risk factors that may predict the development of this important clinical condition.

PMID: 21151627 [PubMed] PMCID: PMC2999510 Free PMC Article

Stesso SNP con risultati contrastanti rispetto a Sarasquete ??

J Oral Pathol Med. 2011 Jul;40(6):510-5. doi: 10.1111/j.1600-0714.2010.01004.x. Epub 2011 Jan 20.

Vascular endothelial growth factor genetic polymorphisms and haplotypes in female patients with bisphosphonate-related osteonecrosis of the jaws.

Arduino PG, Menegatti E, Scoletta M, Battaglio C, Mozzati M, Chiecchio A, Berardi D, Vandone AM, Donadio M, Gandolfo S, Scully C, Broccoletti R.

Department of Biomedical Sciences and Human Oncology, Oral Medicine Section, University of Turin, Turin, Italy. paolo.arduino@gmail.com

Abstract

OBJECTIVE: To investigate the polymorphisms of the vascular endothelial growth factor (VEGF) gene in relation to female patients who developed bisphosphonate-related osteonecrosis of the jaws (BRONJ).

METHODS: Test subjects were 30 Italian female patients with BRONJ (Group A). Control subjects were 30 female patients with a history of intravenous bisphosphonate use without any evidence of osteonecrosis (Group B) and 125 unrelated healthy volunteers (Group C). Three single-nucleotide polymorphisms were investigated: -634 G>C, occurring in 5' untranslated region (UTR); +936 C>T, occurring in 3' UTR; and -2578 C>A of the promoter region.

RESULTS: The frequency of the VEGF CAC (+936/-2578/-634) haplotype was increased in patients with BRONJ, compared with female disease-negative controls [odds ratio (OR) = 2.76, 95% CI = 1.09-4.94, P = 0.039; corrected P value: P(c) = 0.117], and was also increased compared with female healthy controls (OR = 2.11, 95% CI = 1.14-3.89, P = 0.024; corrected P value: P(c) = 0.072). The CC homozygotes of -634G>C of VEGF gene and AA homozygotes of -2578C>A have also been significantly correlated in female patients who developed BRONJ compared with healthy controls (OR = 2.04, 95% CI = 1.12-3.70, P = 0.008; corrected P value: P(c) = 0.024).

CONCLUSIONS: These results suggest a possible haplotype effect of VEGF polymorphisms expression in BRONJ Italian female patients. Studies with different and larger populations possibly using TagSNP to represent all haplotypes within the VEGF gene are needed to further delineate the genetic contribution of this gene to BRONJ.

PMID: 21251073 [PubMed - in process]

Molto mirato sul VEGF, c'è qualche significatività di risutato ma campione piccolo e molto omogeneo

MARCATORI DEL TURN OVER OSSEO

MARCATORI DEL TURN OVER OSSEO

DEPOSIZIONE :

SANGUE

- OSTEOCALCINA
- FOSFATASI ALCALINA TOTALE
- FOSFATASI ALCALINA OSSEA
- PEPTIDE C-TERMINALE PROCOLLAGENE I

RIASSORBIMENTO :

SANGUE

- FOSFATASI ACIDA (TRAP)
- CROSS-LINKS : DPD, CTx, NTx

URINA

- CROSS-LINKS : CTx, NTx
- IDROSSIPROLINA A DIGIUNO
- CALCIURIA A DIGIUNO
- GLICOSIDI DELLA IDROSSILISINA

PREVENZIONE DEI RISCHI?

Telopeptide C-terminale del collageno I (CTx) (urine, siero) :

- misura il turnover osseo
- misura uno specifico crosslink di un peptide del collagene di tipo I

SERUM CTX TESTING (a digiuno)

- 300 pg/mL: valori normali

DRUG HOLIDAY (6 mesi)

30-102 pg/mL ➛ 162-343 pg/mL

Marx *et al*, J Oral Maxillofac Surg 2007; **65**: 2397-2410.

PREVENZIONE DEI RISCHI?

SERUM CTX TESTING (a digiuno)

- VALORI > 150 pg/mL
- VALORI < 150 pg/mL (drug holiday 4-6/12)

Valore CTX	Rischio di ONJ
300-600 pg/mL (normale)	nessuno
150-299 pg/mL	minimo
101-149 pg/mL	moderato
< 100 pg/mL	alto

Marx *et al*, J Oral Maxillofac Surg 2007; **65**: 2397-2410.

J Oral Maxillofac Surg. 2010 Sep;68(9):2241-7.

Serologic bone markers for predicting development of osteonecrosis of the jaw in patients receiving bisphosphonates.

Lazarovici TS, Mesilaty-Gross S, Vered I, Pariente C, Kanety H, Givol N, Yahalom R, Taicher S, Yarom N.

Resident, Department of Oral and Maxillofacial Surgery, Sheba Medical Center, Tel-Hashom

Abstract

PURPOSE: Osteonecrosis of the jaw is a well-documented side effect of bisph onate (BP) use. mpts have recently been made to predict the development of bisphosphonate-related osteonecrosis of the jaw (BRONJ). We prospectively investigated the predictive value of serum lev C-terminal telopeptide of collagen I (CTX), bone-specific alkaline phosphatase, and parathyroid hormone for the development of BRONJ.

PATIENTS AND METHODS: Data on the demographics, comorbidities, and BP treatment w ollected from 78 patients scheduled for dentoalveolar surgery. Of the 78 patients, 51 had been treated with oral BPs and 27 had been treated with frequent intravenous infusions of BPs d samples for CTX, bone-specific alkaline phosphatase, and parathyroid hormone measurements were taken preoperatively. Surgery was performed conservatively, and antibiotic medica were prescribed for 7 days.

RESULTS: Of the 78 patients, 4 patients taking oral BPs (7.8%) and 14 receiving intravenous BPs (51.8%) developed BRONJ. A CTX level less than 150 pg/mL was significantly associated with BRONJ development, with an increased odds ratio of 5.268 (P = .004). The bone-specifi line phosphatase levels were significantly lower in patients taking oral BPs who developed BRONJ. The parathyroid hormone levels were similar in patients who did and did not de BRONJ.

CONCLUSION: The incidence of BRONJ after oral surgery involving bone is greater among patients receiving frequent, intravenous infusions of BPs than among patients taking oral BPs. Although the measurement of serum levels of CTX is not a definitive predictor of the development of BRONJ, it might have an important role in the risk assessment before oral surgery.

PMID: 20728033 [PubMed - indexed for MEDLINE]

MeSH Terms, Substances

LinkOut - more resources

2011: non esistono marcatori sicuri predittivi di nessun tipo!

PROCEDURE PREVENTIVE

Necessità di prevenzione di ONJ:

Trattamento dei siti di infezione attiva (bonifica) prima del trattamento con bifosfonati :

CORREZIONE FATTORI PREDISPONENTI

eliminazione di “siti a rischio”

- Educazione del paziente ad una corretta igiene orale
- ottimizzazione dello stato di salute parodontale
- ispezione frequente del cavo orale
- esecuzione di RX panoramica dentaria
- visite odontoiatriche periodiche

ANAMNESI MEDICA

- **HA AVUTO UNA NEOPLASIA NEGLI ULTIMI 5 ANNI ?**
- **HA EFFETTUATO CHEMIOTERAPIA ?**
- **SOFFRE DI OSTEOPOROSI ?**
- **QUALI FARMACI ASSUME ESATTAMENTE ?**
- **QUALI FARMACI HA ASSUNTO PER LUNGO TEMPO NEGLI ULTIMI 2 ANNI ?**

1: Ann Oncol. 2008 Jul 22. [Epub ahead of print]

Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan.

Ripamonti CI, **Maniezzo M**, **Campa T**, **Fagnoni E**, **Brunelli C**, **Saibene G**, **Bareggi C**, **Ascani L**, **Cislaghi E**.

Palliative Care Unit (Pain Therapy and Rehabilitation).

BACKGROUND: Screening of the oral cavity and dental care was suggested as mandatory preventive measures of osteonecrosis of the jaw (ONJ) in patients receiving bisphosphonates (BPs). We investigated the occurrence of ONJ before and after implementation of dental preventive measures when starting BP therapy. PATIENTS AND METHODS: Since April 2005, 154 consecutive patients treated with BPs (POST-Group) have undergone a baseline mouth assessment (dental visit +/- orthopantomography of the jaws) to detect potential dental conditions and dental care if required. A retrospective review was also conducted of all consecutive cancer patients with bone metastases (PRE-Group) and treated for the first time with BPs from January 1999 to April 2005 in our clinic without receiving any preventive measure. Incidence proportion and incidence rate (IR) were used to estimate the incidence of ONJ. RESULTS: Among the study population (966 patients; male/female = 179/787), 73% had breast cancer. 25% of patients were given zoledronic acid (ZOL), 62% pamidronate (PAM), 8% PAM followed by ZOL and 5% clodronate. ONJ was observed in 28 patients (2.9%); we observed a reduction in the incidence of ONJ from 3.2% to 1.3%, when comparing-pre and post-implementation of preventive measures programme. Considering the patients exposed to ZOL, the performance of a dental examination and the application of preventive measures led to a sustained reduction in ONJ IR (7.8% in the PRE-Group versus 1.7% in the POST-Group; P = 0.016), with an IR ratio of 0.30 (95% confidence interval 0.03-1.26). CONCLUSIONS: ONJ is a manageable and preventable condition. Our data confirm that the application of preventive measures can significantly reduce the incidence of ONJ in cancer patients receiving BPs therapy. Dental exams combined to the identification of patients at risk in cooperation with the Dental Team can improve outcomes and increase the number of ONJ-free patients.

Ann Oncol. 2011 Mar 22. [Epub ahead of print]

Impact of dental care in the prevention of bisphosphonate-associated osteonecrosis of the jaw: a single-center clinical experience.

Vandone AM, Donadio M, Mozzati M, Ardine M, Polimeni MA, Beatrice S, Ciuffreda L, Scoletta M.

Department of Medical Oncology and Hematology, C.O.E.S. Subalpine OncoHematology Cancer Center.

Abstract

BACKGROUND: Osteonecrosis of the jaw (ONJ) is associated with bisphosphonate (BP) therapy and invasive dental care. An Interdisciplinary Care Group (ICG) was created to evaluate dental risk factors and the efficacy of a preventive restorative dental care in the reduction of ONJ risk.

PATIENTS AND METHODS: This prospective single-center study included patients with bone metastases from solid tumors. Patients who received at least one BP infusion between October 2005 and 31 August 2009 underwent one or more ICG evaluation and regular dental examinations. We also retrospectively evaluated patients with bone metastases from solid tumors who did not undergo dental preventive measures.

RESULTS: Of 269 patients, 211 had received at least one infusion of BP therapy: 62% were BP naive and 38% had previous BP exposure. Of these 211 patients followed for 47 months, 6 patients developed ONJ (2.8%). Of 200 patients included in the retrospective analysis, 11 patients developed ONJ (5.5%).

CONCLUSIONS: In comparison with published ONJ rates and those extrapolated from the retrospective analysis, the observed ONJ rate in the prospective group was lower, suggesting that implementation of a preventive dental program may reduce the risk of ONJ in metastatic patients treated with i.v. BP therapy.

PMID: 21427065 [PubMed - as supplied by publisher]

PROCEDURE PREVENTIVE

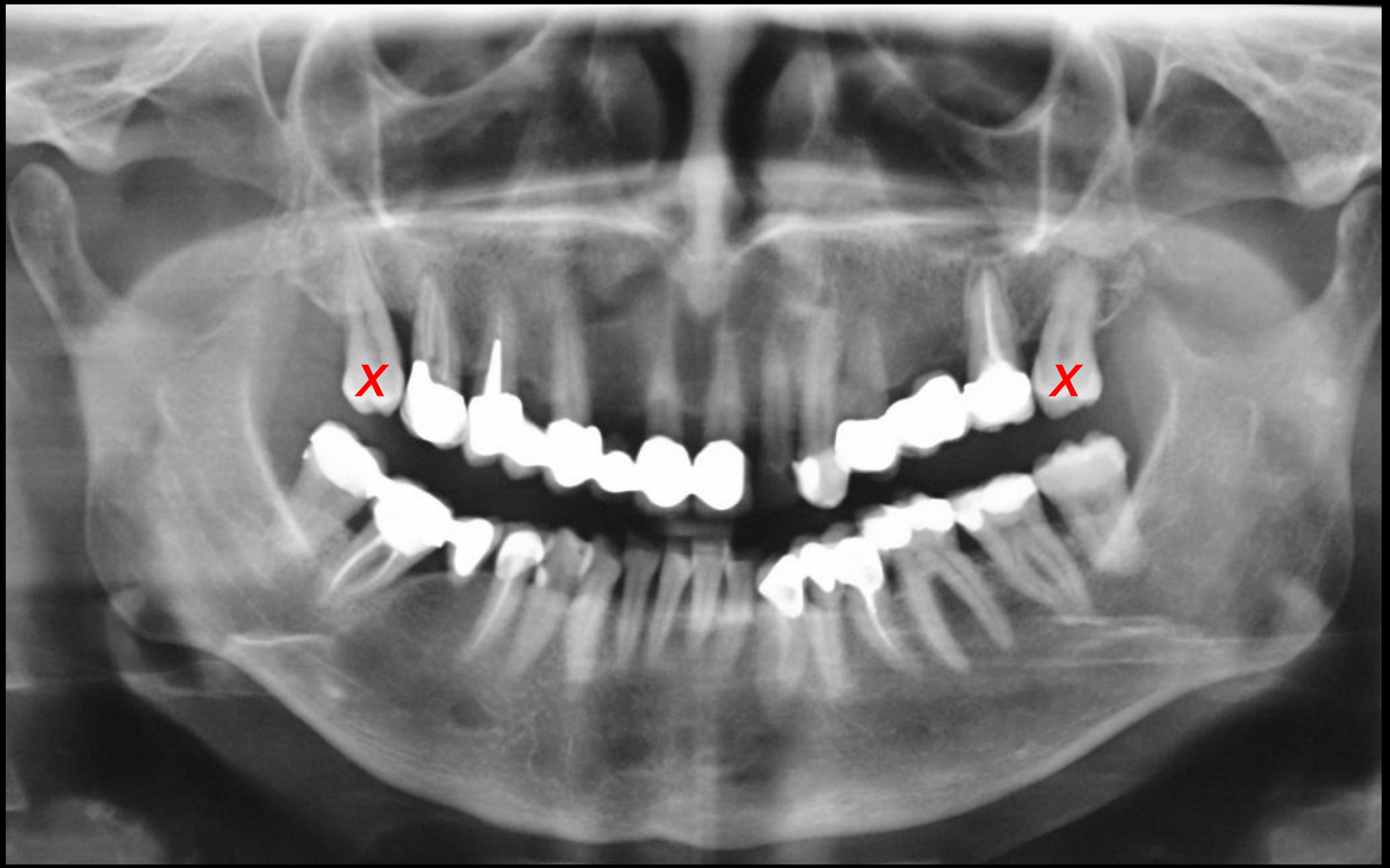
Pz in attesa di iniziare una terapia con bifosfonati e.v.:

PREVENZIONE :

- SENSIBILIZZAZIONE DEL PAZIENTE SULLA NECESSITA' DIEL MANTENIMENTO DI CORRETTA IGIENE ORALE E SUL POTENZIALE RISCHIO DI ONJ : INFORMAZIONE !!!!
- ESTRAZIONE DI OGNI DENTE "PERSO" : iniziare la terapia BF dopo 3-4 settimane dall'ultima estrazione o quando si è raggiunta un'adeguata guarigione chirurgica
- COMPLETARE OGNI PROCEDURA INVASIVA
- COMPLETARE UNA CORRETTA TERAPIA ENDODONTICA E CONSERVATIVA
- PZ CON PROTESI MOBILI: esame mucose (flangia linguale !!!) – controllo compressioni
- DTR ogni 3-4 mesi + TERAPIA CAUSALE
- CONTROLLO RX ogni 6 mesi

Vandone et al, Annals of Oncology 2011

Ripamonti et al, Annals of Oncology 2008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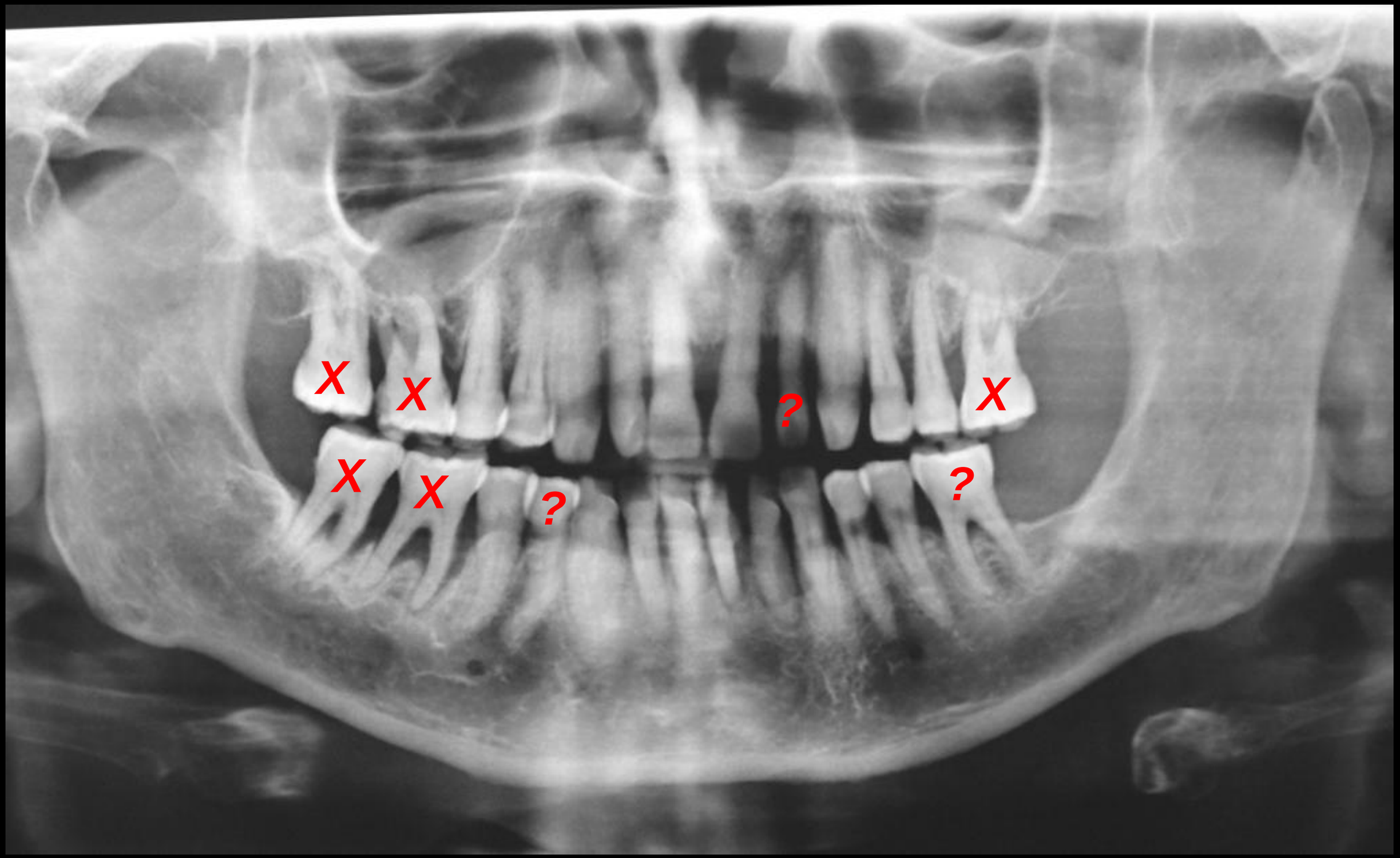
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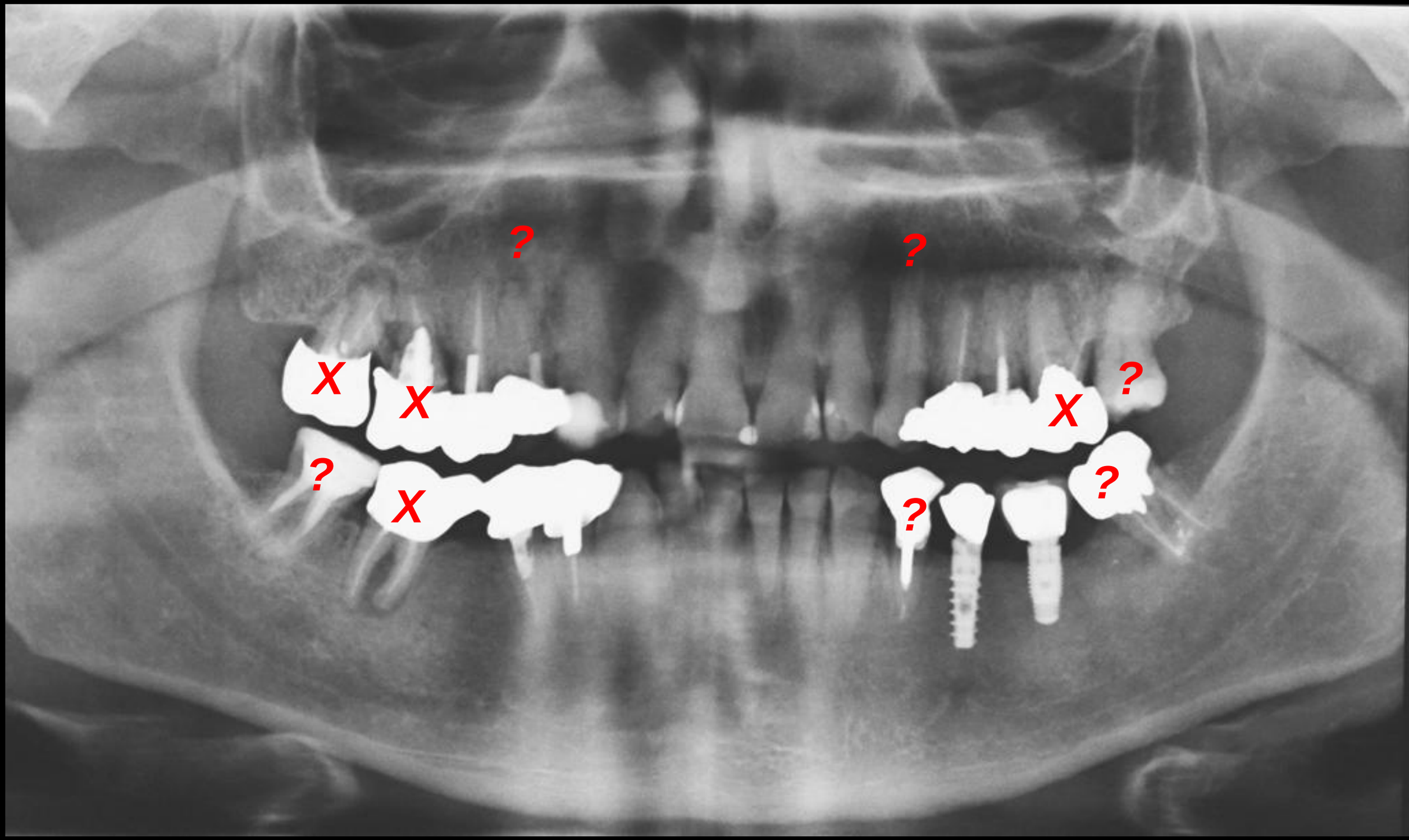
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J Oral Maxillofac Surg. 2011 Feb;69(2):456-62. Epub 2010 Dec 3.

Initial experience on the outcome of teeth extractions in intravenous bisphosphonate-treated patients: a cautionary report.

Scoletta M, Arduino PG, Pol R, Arata V, Silvestri S, Chiecchio A, Mozzati M.

Department of Clinical Physiopathology, Lingotto Dental School, Turin, Italy.

Abstract

PURPOSE: More cases of osteonecrosis of the jaws in patients treated with intravenous bisphosphonates have been reported. The aim of this prospective hospital-based study was to detail a surgical protocol for teeth extraction in such patients.

PATIENTS AND METHODS: Prospective patients with a follow-up of at least 4 months were included. A surgical procedure using an ultrasonic surgical apparatus (Mectron Piezosurgery Device, Mectron Medical Technology, Carasco, Italy) was undertaken. Healing was stimulated by filling the extraction site with autologous plasma rich in growth factors (PRGF System, BTI Biotechnology Institute, Vitoria, Spain). Local and systemic infection controls were also obtained with antibiotic therapy.

RESULTS: Sixty-four patients took part in the study. Two hundred twenty teeth extractions were performed in a surgical setting. Bisphosphonate-related osteonecrosis of the jaw occurred in 5 postextraction sites (2.27%); no statistical differences could be reported regarding age, gender, duration of bisphosphonate treatment, concomitant corticosteroid therapy, mean surgical time, and patients' underlying diseases. In contrast, the mandible appeared to be at greater risk than the maxilla to develop bisphosphonate-related osteonecrosis of the jaw (P = .0342).

CONCLUSIONS: Even with many limitations, the proposed surgical protocol appears to be a possible choice for patients treated with intravenous bisphosphonates who need teeth extraction. Further prospective, possibly randomized studies are necessary to determine if this statement would be the same with larger patient samples in different clinical settings.

PMID: 21129835 [PubMed - indexed for MEDLINE]

UNITO

PREVENZIONE BRONJ

pz oncologici ed ematologici

- Prima di iniziare la terapia con BP
- Dopo aver iniziato la terapia con BP