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RECENT ISSUES :

RISCHIO DI ONJ IN PAZIENTI ONCOLOGICI ED EMATOLOGICI TRATTATI CON FARMACI BIOLOGICI ("TARGET THERAPY")

Alessandria

23 giugno 2009

Vittorio Fusco **SOC Oncologia**

Az. Ospedaliera di Alessandria

ONJ (osteonecrosis of jaws)

" GRANDE

E' IL DISORDINE

SOTTO IL CIELO… "

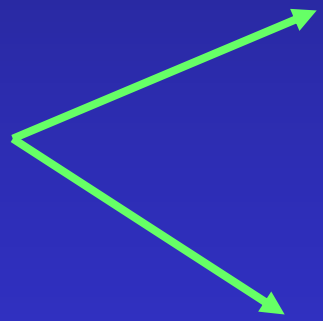
Dicembre 2002 : primo caso di ONJ segnalato alla Novartis

2003-2004 : primi reports in letteratura

Da allora incremento progressivo delle segnalazioni

Clinici utilizzatori di BP

ONJ pone DOPPIO RISCHIO



“DEMONIZZAZIONE” dei BP
(→ più alto rischio di SRE)

“BANALIZZAZIONE”
del rischio di ONJ
(→ mancata prevenzione)
(→ più alto rischio di ONJ)

ONJ correlata ai bifosfonati

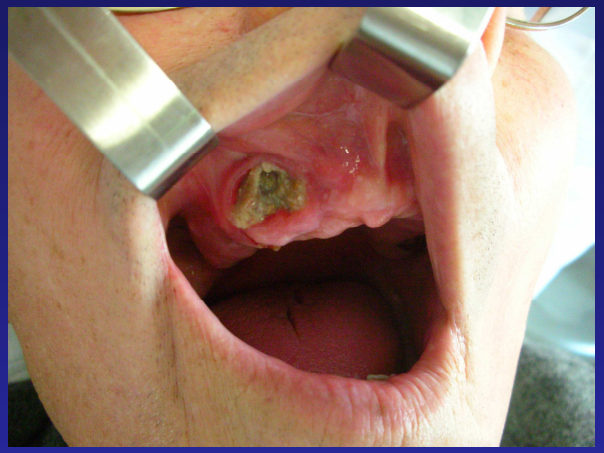
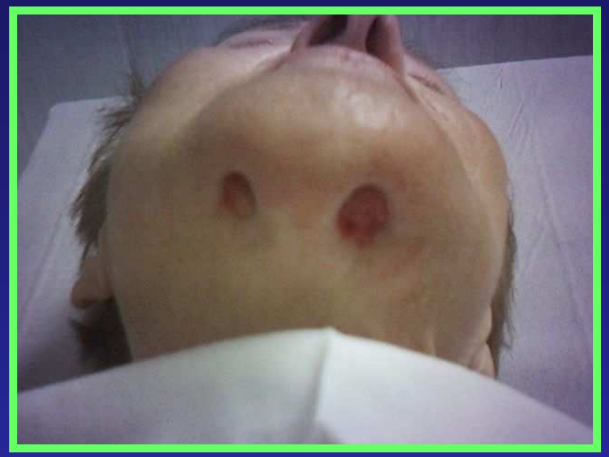


FIGURE 1. Exposed necrotic maxillary bone in a patient receiving zolendronic acid for 6 months. The patient had posterior maxillary extractions performed 4 months earlier. (Courtesy of Dr Jay Neugarten, New Hyde Park, NY.)



Ampia variabilità in

-modalità di esordio (durante e dopo BP)

-sintomaticità (dolore, infezioni, ecc.)

-decorso clinico (spontaneo / dopo terapia)

ONJ

- Definizione ??
- Quadro e decorso clinico ! (variab)
- Epidemiologia ???
- Staging ??
- Fattori di rischio ??
- Etiopatogenesi ?????

Etiopatogenesi della ONJ : MULTIFATTORIALE ?

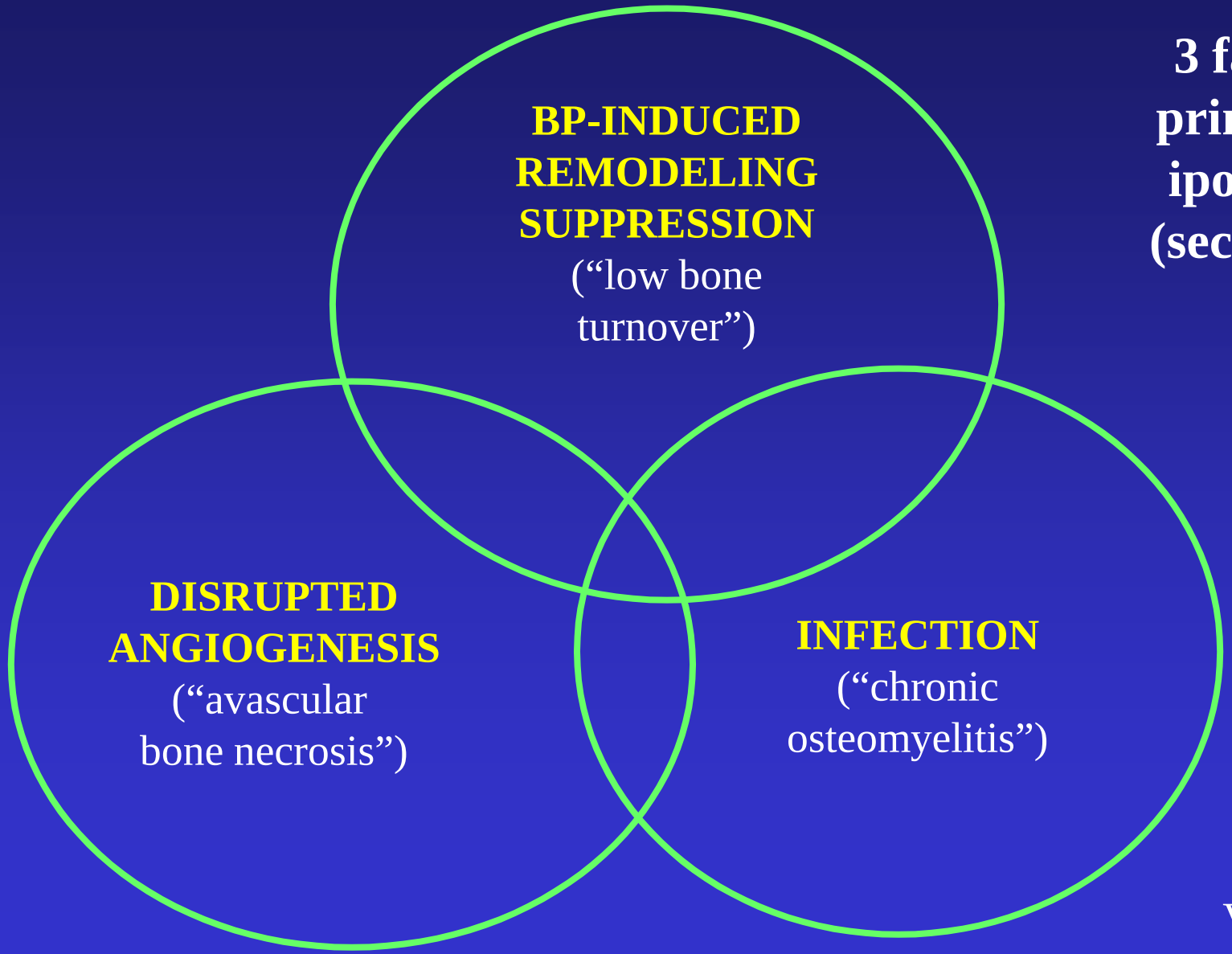
Bisphosphonates and osteomyelitis of the jaw: a pathogenic puzzle.
Bertoldo F, Santini D, Lo Cascio V.
Nat Clin Pract Oncol. 2007 Dec;4(12):711-21. Review.

Pathophysiology, risk factors and management of bisphosphonate-associated osteonecrosis of the jaw: Is there a diverse relationship of amino- and non-aminobisphosphonates?
Diel IJ, et al
Crit Rev Oncol Hematol. 2007 Dec;64(3):198-207. Epub 2007 Sep 12. Review.

Bisphosphonates and osteonecrosis of the jaw: moving from the bedside to the bench.
Allen MR.
Cells Tissues Organs. 2009;189(1-4):289-94. Epub 2008 Aug 13. Review.

Osteonecrosis of the jaw: who gets it, and why?
Reid IR.
Bone. 2009 Jan;44(1):4-10. Epub 2008 Oct 7. Review.

ONJ : IPOTESI ETIOPATOGENETICHE



3 fattori principali ipotizzati (sec. Allen)

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Allen MR, Cells Tissues Organs 2009

The most commonly proposed mechanisms for ONJ …

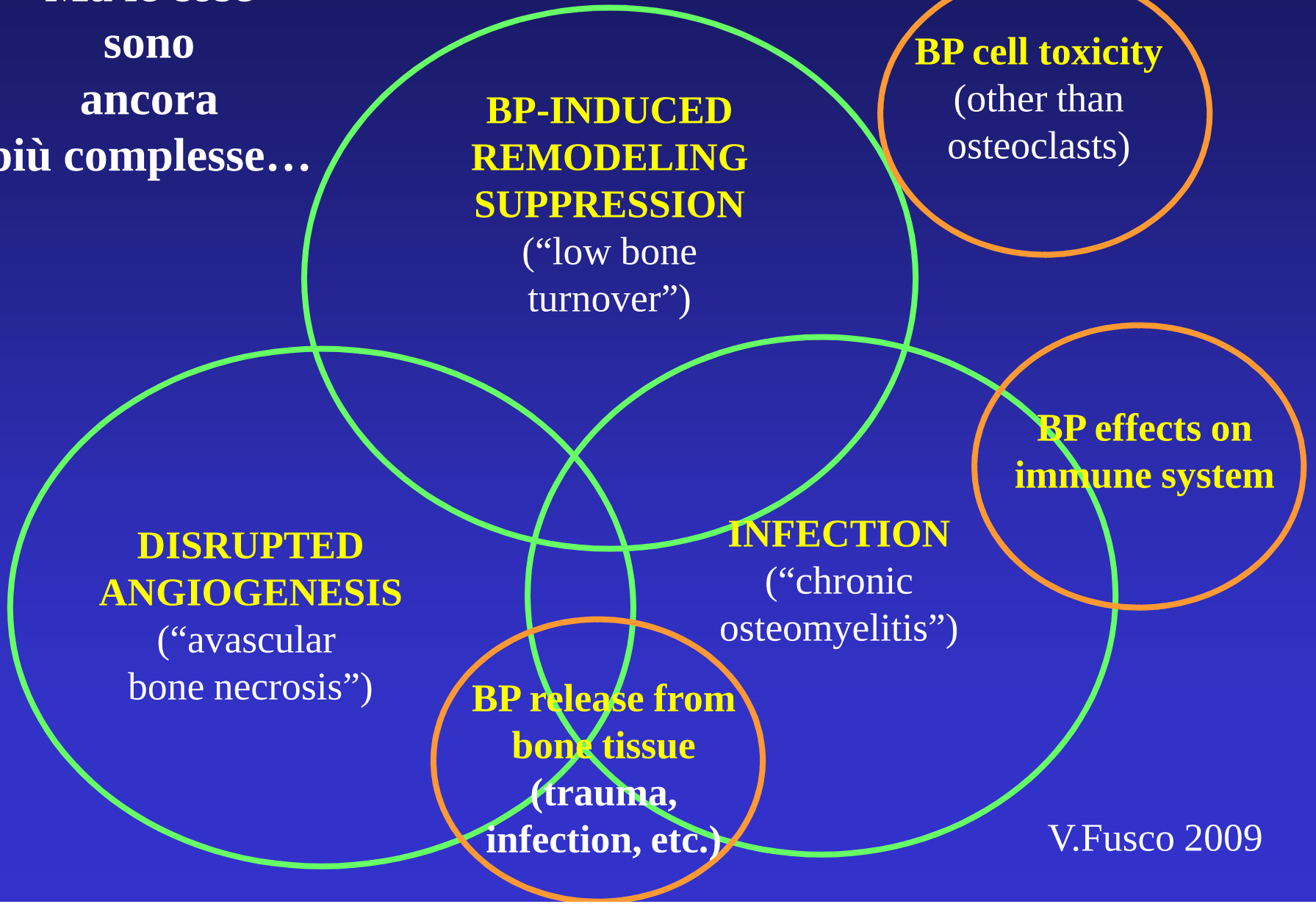
-Remodelling suppression,
-Disrupted angiogenesis, and
-Infection

Most supportive data for each of these are either indirect or nonexistent

→ ***Necessità di studi ulteriori e di modelli animali !!***

ONJ : IPOTESI ETIOPATOGENETICHE

Ma le cose sono ancora più complesse…



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ONJ : IPOTESI ETIOPATOGENETICHE - 1

BP-INDUCED REMODELING SUPPRESSION ("low bone turnover")

A FAVORE

-Rischio di ONJ + alto con BP + potenti
-BP alte dosi / iv (cancer pts) : soppressione maggiore che con basse dosi (osteoporosi)
-Livello di soppressione sito-specifico (MAX in mascellari, specie alveolare)
-Microtraumi → alto turnover → maggiore concentrazione di BP nei mascellari
-Il tasso di rimodellamento aumenta con infezione e dopo intervento odontoiatrico
-Modello animale (ratto)(Pozzato, ASH'08)

CONTRO

-Zone di osso ricche di osteoclasti (Reid, Bone 2009)
-Reperti scintigrafici "a coccarda" (Abu-id)

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ONJ : IPOTESI ETIOPATOGENETICHE - 2

CONTRO

-Non evidenza di vascolatura ridotta in osso necrotico (Hansen)
-Il tessuto sanguina alla chirurgia
-Modello animale (beagle)(Allen JOMS 2009)
-Effetto antiangiogenetico dei BP NON su osso o midollo osseo
-Clodronato usato in ORN (dopo RT)
-Alendronato usato in Necrosi Femorale

A FAVORE

-Effetto antiangiogenetico dei BP (varie colture, tessuti, modelli animali)
-Effetto "antiangiogenetico" dei BP su mucosa/ tessuti molli/ cicatrici (dopo estrazione)
-Recenti casi di ONJ dopo bevacizumab (da solo e con BP) e altri agenti biologici ("target")
-Ridotti livelli sierici di IL-17 (Oteri)
-Dati di Kapitola 1998 e 2000, e Wood 2002

DISRUPTED ANGIOGENESIS
("avascular bone necrosis")

INCERTI

- Dati contrastanti su BP + Thalidomide

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ONJ : IPOTESI ETIOPATOGENETICHE - 3

A FAVORE

-Flora batterica + Infezione post-estrattiva + Immunosoppressione (cancer pts) (Hansen 2006)

-Biopsie alveolari durante estrazione in paz in terapia con BP, senza ONJ (solo quelli con osteomielite sottostante vanno incontro a ONJ)(Saia, Bologna 2008)

CONTRO

-Infezione di tessuto già necrotico (Yarom 2007)

-Infezione su ritardata guarigione di tessuti molli (post-estrattiva)

-Modello animale (beagle dog): infezione può contribuire, ma non è necessaria alla ritardata cicatrizzazione (Allen)

INFECTION
("chronic osteomyelitis")

CONTRO / A FAVORE

-Effetto dei BP su immunità: reports contraddittori

-Alcuni → ridotta (+/-linfocitopenia), altri → rafforzata

-Reazione di fase acuta da BP ev

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ONJ : IPOTESI ETIOPATOGENETICHE - 4

A FAVORE

-Tossicità su cellule endoteliali, fibroblasti, ecc

- Modello con Keratinociti

BP cell toxicity (other than osteoclasts)

CONTRO / A FAVORE

-Effetto dei BP su cell. immunitarie: reports contraddittori

-Alcuni → ridotta (+/-linfocitopenia), altri → rafforzata

-Reazione di fase acuta da BP ev

BP effects on immune system

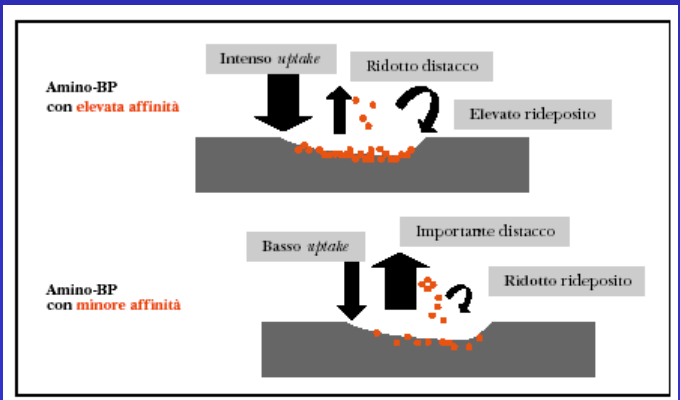

Figura 10.
Lo schema rappresenta la possibilità di riattivazione e "ricircolo" locale, per opera della riattivazione del *turnover* osseo, che è alla base della persistenza di effetto degli amino-bisfosfonati

(Modificata da: Nancollas GH et al *Bone* 2006; 38:617-627)

BP release from bone tissue (trauma, infection, etc.)

da Bertoldo 2007

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ONJ : IPOTESI ETIOPATOGENETICHE - 2

CONTRO

-Non evidenza di vascolatura ridotta in osso necrotico (Hansen)
-Il tessuto sanguina alla chirurgia
-Modello animale (beagle)(Allen JOMS 2009)
-Effetto antiangiogenetico dei BP NON su osso o midollo osseo
-Clodronato usato in ORN (dopo RT)
-Alendronato usato in Necrosi Femorale

DISRUPTED ANGIOGENESIS
("avascular bone necrosis")

A FAVORE

-Effetto antiangiogenetico dei BP (varie colture, tessuti, modelli animali)
-Effetto "antiangiogenetico" dei BP su mucosa/ tessuti molli/ cicatrici (dopo estrazione)
-Recenti casi di ONJ dopo bevacizumab (da solo e con BP) e altri agenti biologici ("target")
Ridotti livelli sierici di IL-17 (Oteri)
-Dati di Kapitola 1998 e 2000, e Wood 2002

INCERTI

- Dati contrastanti su BP + Thalidomide

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Dati vecchi e nuovi

- Thalidomide in pazienti con Mieloma
- Trial di Aragon-Ching in ca. prostatico
- ONJ da Bevacizumab da solo (senza BP)
- ONJ da BP + farmaci biologici “target”

Thalidomide in pazienti con Mieloma : 2/7 studi

Badros (JCO 2006)	90 paz con MM (ONJ in 22/90) Non aumento di RR per Thal
Zervas (BJH 2006)	303 paz con MM (ONJ in 28/254) RR 2.4 per Thal
Tosi (Blood 2006)	259 paz con MM (ONJ in 9)(6.6% a 2 anni)* RR non aumentato da Thal **(follow-up breve)*
Pozzi (Leuk Lymph 2007)	28 casi di ONJ in MM = 1.9% (underestimated) RR aumentato da Thal
Boonyapakorn (Oral Oncol 2008)	80 paz totali ; ONJ in MM = 10/58 Non RR aumentato da Thal e Bortezomib
Dimopoulos (Ann Oncol 2009)	128 paz con MM, tutti trattati con Zometa ONJ in 10/28 (senza prev.) vs 6/90 (con prev.) Non RR aumentato da Thal e Bortezomib

Hoff (JBMR 2008) 13 casi di ONJ in 548 paz con MM (2.4%). Non effetto di Thal

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Aragon-Ching (ASCO 2007) : paz con ca prostata

Schema di terapia : ATTP (bevacizumab, docetaxel, thalidomide, prednisone) + Zometa

→ ONJ in 6 / 36 pts (17%)

The Oncologist®
Letters to the Editor

Osteonecrosis of the Jaw and the Use of Antiangiogenic Agents: Just an Association?

JEANNY B. ARAGON-CHING,[a] WILLIAM L. DAHUT[b]

[a]George Washington University Medical Center, Washington, DC, USA; [b]Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Cancer Invest. 2009 February ; 27(2): 221–226. doi:10.1080/07357900802208608.

Higher incidence of osteonecrosis of the jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents

Jeanny B. Aragon-Ching[1], Yang-Min Ning[1], Clara C. Chen[2], Lea Latham[1], Jean-Pierre Guadagnini[3], James L. Gulley[1], Philip M. Arlen[1], John J. Wright[4], Howard Parnes[5], William D. Figg[6], and William L. Dahut[1,*]

1 *Medical Oncology Branch, National Cancer Institute, Bethesda, MD 20892, USA*

• Aragon Ching, Cancer Invest 2009

ONJ is an important toxicity in cancer patients receiving bisphosphonate therapy. Here we report a higher than usual incidence of ONJ, 11 of 60 (18.3%, 95% Confidence Interval, CI: 9% – 28%) patients enrolled in a phase II clinical trial combining bevacizumab, docetaxel, thalidomide, and prednisone (ATTP) in chemotherapy-naïve men with metastatic castration resistant prostate cancer (mCRPC). The use of bisphosphonates was allowed at study entry. Our study suggests that anti-angiogenic and chemotherapy agents can predispose to the development of ONJ in men with mCRPC on zoledronic acid. Imaging modalities, such as bone scans, may be useful in following the clinical course of patients who develop ONJ.

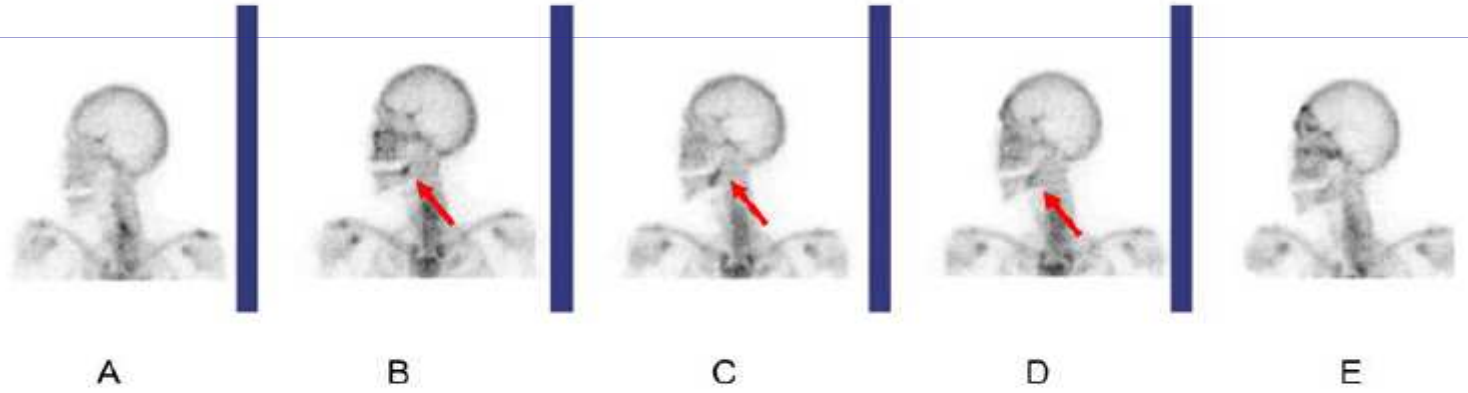

Figure 1.
Patient number 6 showing a negative bone scan upon study enrollment (A); Positive uptake over the left mandibular area appeared approximately 6 weeks prior to ONJ diagnosis (B); Increasing (worsening) uptake over the left mandibular area noted 4 months later (C); Improvement in the intensity noted after 4 months (D); Resolution and return to baseline 6 months later.

ONJ in 11/53 trattati con Z (20%)

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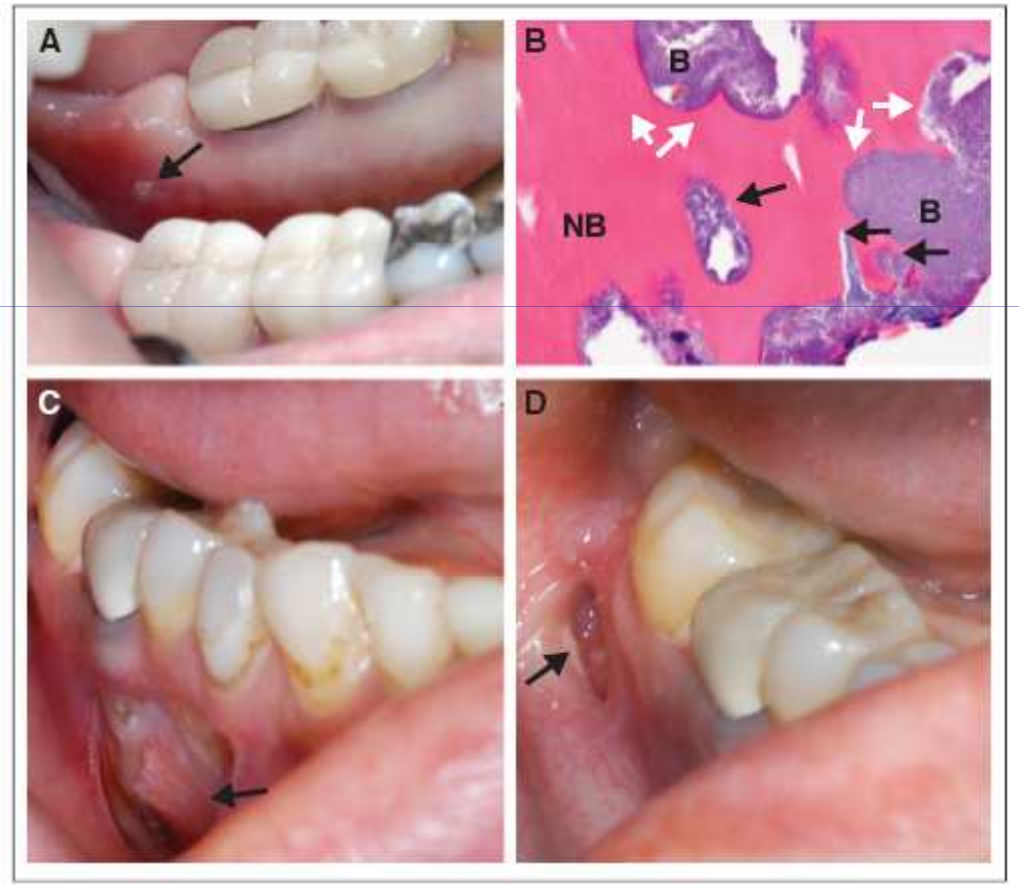
ONJ da Bevacizumab da solo (senza BP)

VOLUME 26 · NUMBER 24 · AUGUST 20 2008

JOURNAL OF CLINICAL ONCOLOGY

DIAGNOSIS IN ONCOLOGY

Osteonecrosis of the Jaw Related to Bevacizumab



2 casi di ONJ in pazienti Trattati con Avastin (Bevacizumab) e NON con BPs

(1 tumore mammario, 1 glioblastoma m.)

V.Fusco

ONJ da Bevacizumab da solo (senza BP)

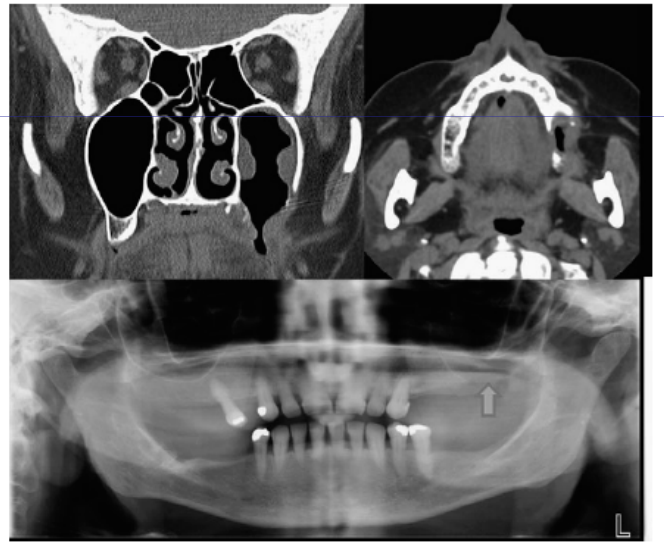
Annals of Oncology Advance Access published October 31, 2008

letter to the editor

Annals of Oncology

Bevacizumab-associated osteonecrosis of the jaw

A 63-year-old woman suffered a local relapse of breast cancer. Baseline bone scan was normal and she had never received bisphosphonates previously. While being treated with liposomal doxorubicin and bevacizumab, she experienced left-sided maxillary pain after 1 month of therapy. A tooth infection was diagnosed and teeth number 25 and 26 were extracted. One month later, a mouth-antrum fistula was surgically revised and occluded. Shortly afterward the patient suffered from a trigeminal neuralgia. X-ray and computed tomography scan showed maxillary sinusitis and signs of osteonecrosis of the jaw (ONJ; Figure 1). The jaw lesion was carefully extirpated and the maxillary sinus was drained. Histological work-up verified the clinical diagnosis of ONJ, and an infiltration from the cancer was excluded. At 3 months of



1 caso di ONJ in paziente con carcinoma mammario metastatico trattata con Avastin (Bevacizumab) e chemioterapia, ma NON con BPs

V.Fusco

OSTEONECROSI DEI MASCELLARI CORRELATA ALLA TERAPIA CON BEVACIZUMAB: CASE-REPORT

A.Decensi*, S.Zanardi*, C.Caroti*, A.Gozza*, M.D'Amico*.
* S.C. Oncologia Medica - E.O. “Ospedali Galliera”, Genova.

P Balbi**, P Brunamonti Binello**.
** S.C. Odontostomatologia E.O. “Ospedali Galliera”, Genova.

Case-report di osteonecrosi secondaria a trattamento antineoplastico con Bevacizumab in un paziente di anni 47 affetto da adenocarcinoma parotideo avanzato.

V.Fusco

ONJ da BP + farmaci biologici “target”

Ayllon, Ann Oncol 2009	**1 caso da BP + Bevacizumab (ca mammella)** **1 caso da BP + Sunitinib (ca renale)**
Brunello, Bone 2009	**1 caso da BP + Sunitinib (ca renale)**
Christodoulou, Oncology 2009	**3 casi da BP + Bevacizumab (2 ca mammella, 1 ca colon)** **1 caso da BP + Sunitinib (ca renale)**
Mc Arthur , ASCO 2008 (abs)	**8 casi da BP + Bevacizumab**

V.Fusco

Osteonecrosis of the jaw under bisphosphonate and antiangiogenic therapies: cumulative toxicity profile?

Both patients received i.v. zoledronate 4 mg every 3 weeks, given for the treatment of bone metastases in our female breast cancer patient (patient 1) and of hypercalcemia in our male renal cell carcinoma patient (patient 2). Patient 1 was switched to oral clodronate after 4 months on zoledronate. She had been on clodronate for 15 months and patient 2 had been on zoledronate for 19 months when ONJ occurred. Patient 1 had received bevacizumab for 2–3 months and patient 2 had received sunitinib for 14 months before diagnosis of ONJ. Both died with ongoing ONJ.

Ayllon, Ann Oncol 2009

1 caso da BP + Bevacizumab (ca mammella)
1 caso da BP + Sunitinib (ca renale)

V.Fusco

Worsening of osteonecrosis of the jaw during treatment with sunitinib in a patient with metastatic renal cell carcinoma

Antonella Brunello [a,*], Giorgia Saia [b], Alberto Bedogni [c], Daniela Scaglione [a], Umberto Basso [a]

[a] Istituto Oncologico Veneto, IOV–I.R.C.C.S. Padova, Italy
[b] Unit of Maxillofacial Surgery, University of Padova, Italy
[c] Section of Oral and Maxillofacial Surgery, University of Verona, Italy

We report on the potential association of suspected bisphosphonate-associated osteonecrosis of the jaw (BRONJ) recurrence with the use of the novel antiangiogenic drug sunitinib. A 59 year-old patient affected by metastatic renal cell carcinoma (RCC) and established BRONJ experienced consecutive episodes of painful jaw infection with cutaneous fistula and bone sequestration which occurred during active treatment with sunitinib, improved after discontinuation and antibiotic therapy, then rapidly worsened with resumption of sunitinib. We hypothesize that the potent antiangiogenic activity of sunitinib may amplify the inhibition of bone remodeling exerted by aminobisphosphonates entrapped within the osteonecrotic mineral matrix, antagonize mucosal healing and expose to infections during treatment. This supports the emerging role of soft-tissue damage in the pathogenesis of osteonecrosis of the jaw.

Brunello, Bone 2009

1 caso da BP + Sunitinib (ca renale)

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Brunello, Bone 2009

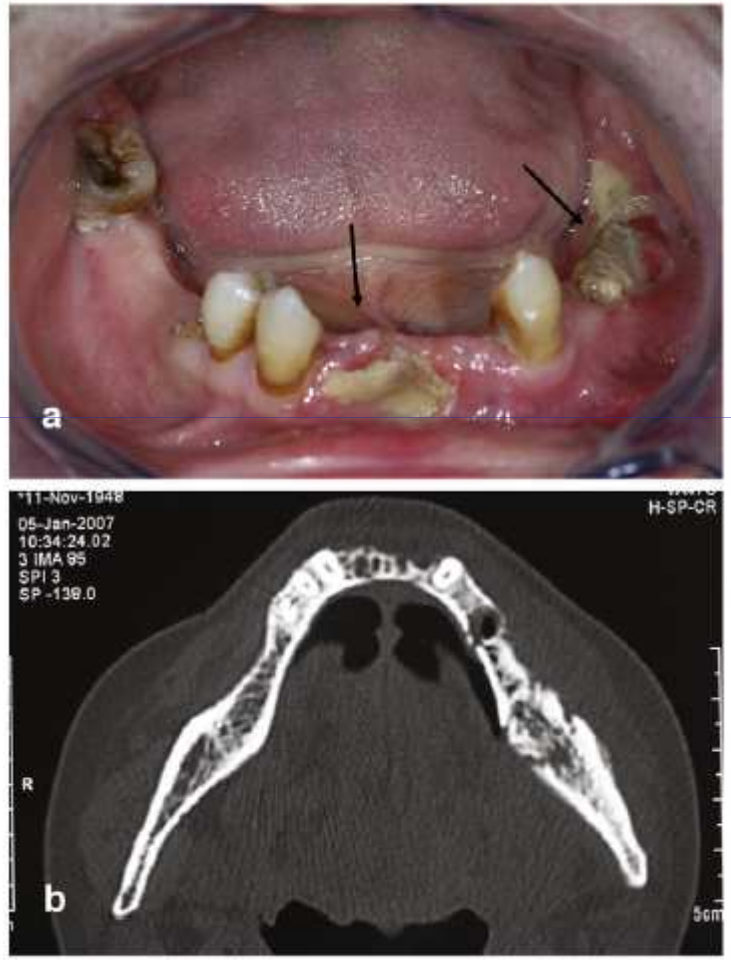

Fig. 1. (a) Exposed necrotic bone, gingival fistulas and purulent discharge (b) Axial mandibular CT scan showing increased bone marrow density and diffuse signs of osteonecrosis/osteomyelitis.

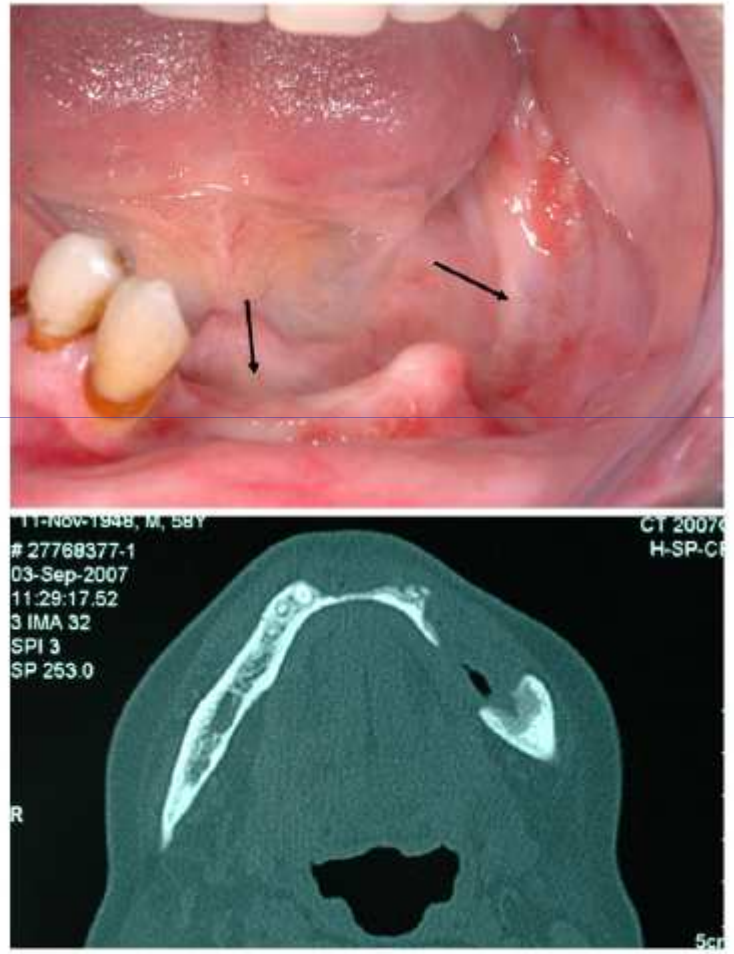

Fig. 3. Situation after cessation of sunitinib and antibiotic therapy: partial repair of gingival tissue surrounding the exposed bone.

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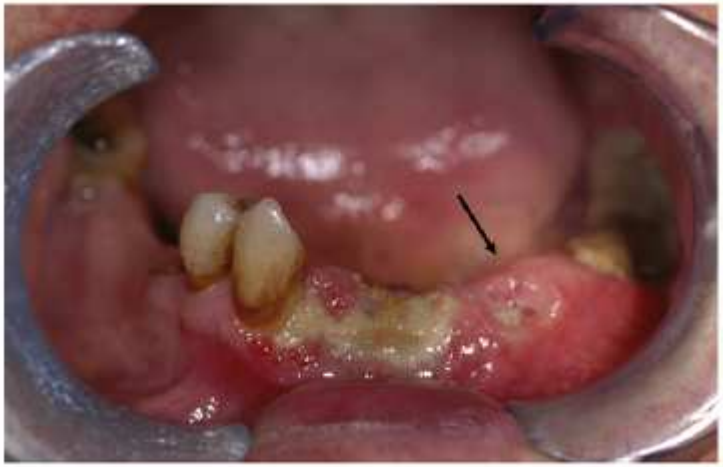
Brunello, Bone 2009



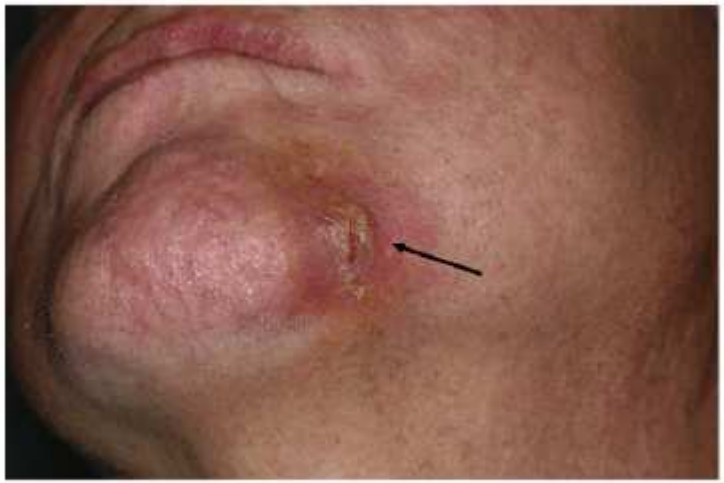


Fig. 2. Situation after resumption of sunitinib: increased exposure of bone, loss of a canine tooth and cervical cutaneous sinus-track formation.

(Fig. 4). The bone infection improved with another cycle of oral amoxicillin–clavulanic acid and metronidazole, and gingival repair occurred.

This is the first report of osteonecrosis of the jaw in a patient receiving a novel antiangiogenic drug who had been previously treated with i.v. bisphosphonates. The consecutive episodes of painful jaw infection with cutaneous fistula and bone sequestration in our patient were likely correlated with sunitinib therapy, occurring during active treatment, significantly improving after sunitinib discontinuation and antibiotic therapy, then rapidly worsening with resumption of treatment.

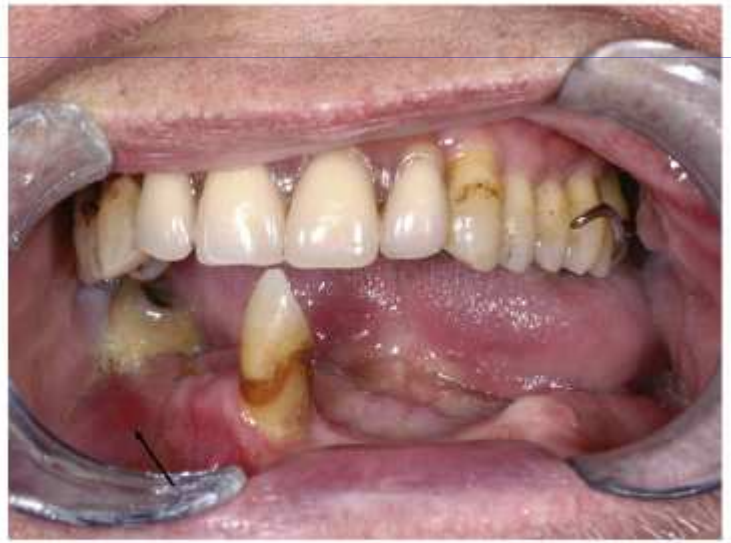


Fig. 4. At sunitinib re-challenge: painful swelling, bone exposure in the right body of the mandible with spontaneous tooth loss.

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Mc Arthur , MSKCC New York
ASCO 2008
abs : 8 casi da BP + Bevacizumab

Slides in www.asco.org: Virtual meeting ASCO 2008

BP senza Bevacizumab **ONJ : 76 su 6534**	**Mediana : 25 mesi**
BP e Bevacizumab **ONJ : 9 su 409**	**Mediana:** **12 mesi da inizio BP** **10 mesi da inizio BEV**
BEV (non BP) **ONJ : 2 su 1711**	**dopo 2.8 e 5.7 mesi**

V.Fusco

Combination of Bisphosphonates and Antiangiogenic Factors Induces Osteonecrosis of the Jaw More Frequently than Bisphosphonates Alone

C. Christodoulou[a, b] A. Pervena[a] G. Klouvas[a] E. Galani[a] M.E. Falagas[b]
G. Tsakalos[a] A. Visvikis[a] A. Nikolakopoulou[a] V. Acholos[a] G. Karapanagiotidis[a]
E. Batziou[a] D.V. Skarlos[a]

[a]Second Oncology Department, Metropolitan Hospital and [b]Alfa Institute of Biomed
Athens, Greece

Abstract

Background: The use of bisphosphonates is associated with osteonecrosis of the jaw (ONJ). Antiangiogenic agents are used with increasing frequency and may induce the risk of ONJ, especially when administered concurrently with bisphosphonates. ***Patients and Methods:*** We retrospectively reviewed data of 116 patients receiving bisphosphonates, 78 zoledronic acid and 38 ibandronic acid, with or without antiangiogenic agents for osseous metastases from various tumors in our department from June 2007 to June 2008. ***Results:*** ONJ developed in: 2 patients with breast cancer and 1 with colon cancer receiving concurrently bisphosphonates and bevacizumab, 1 patient with renal cell carcinoma receiving sunitinib and zoledronic acid concurrently, and 1 patient with prostate cancer receiving zoledronic acid without antiangiogenic agents. The incidences of ONJ among patients receiving bisphosphonates with or without antiangiogenic agents were 16 and 1.1%, respectively. The difference was statistically significant ($p = 0.008$). The treatment duration of

Christodoulou, Oncology 2009

3 casi da BP + Bevacizumab (2 ca mammella, 1 ca colon)
1 caso da BP + Sunitinib (ca renale)

V.Fusco

OSTEONECROSI DEI MASCELLARI (ONJ) IN PAZIENTI IN TERAPIA CON BIFOSFONATI E FARMACI BIOLOGICI ("TARGET"): CASE REPORTS

Chiara Paglino [1], Camillo Porta [1], Ilaria Imarisio [1], Cinzia Canipari [1], Vittorio Fusco [2], Antonella Fasciolo [3], Antonella Pertino [4]

[1] Oncologia Medica, Fondazione IRCCS Policlinico San Matteo, Pavia
[2] SC Oncologia, ASO Alessandria
[3] SC ORL , ASO Alessandria
[4] Day-Hospital Onco-Ematologico, ASO Alessandria

Caso 1 : Sorafenib → Sunitinib + Ibandronato

Caso 2 : Zoledronato + Sorafenib

Caso 3 : Pamidronato + AP235 (inibitore di m-TOR)

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Bisphosphonate- Related ONJ

2002- 2003 : primi casi segnalati (Marx, Ruggiero, ecc.)

Minimizzazione / incredulità

- **rifiuto da major journals**
- **Tarassoff (Novartis)**
  J Oral Max Surg oct 2003 : critiche a Marx (sept 2003)

2009 : migliaia di casi; necessità di prevenzione

Target therapy-related ONJ

2008 : primi casi segnalati (Estilo 2008, ecc)

?

il “take home message”

è . . .

Non dormiamoci sopra … !