OSTEONECROSI (ONJ) E MIELOMA

Torino
16 maggio 2019

Vittorio Fusco SC Oncologia
Az. Ospedaliera di Alessandria

Gruppo di Studio ONJ

SC Oncologia

CENTRO di DOCUMENTAZIONE sulla OSTEONECROSI

osteonecrosi@ospedale.al.it

Tel 0131- 206753 o 0131- 206052

g.c. dott.ssa Maria Teresa Foco

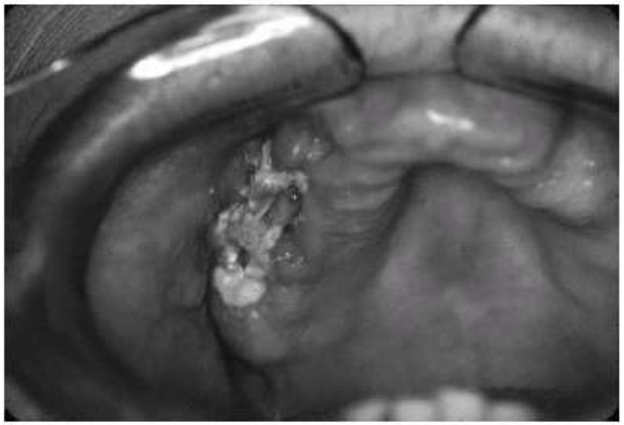


FIGURE 1. Exposed necrotic bone in the mandible in a patient who was taking pamidronate (Aredia). Exposed bone initiated by a tooth removal.

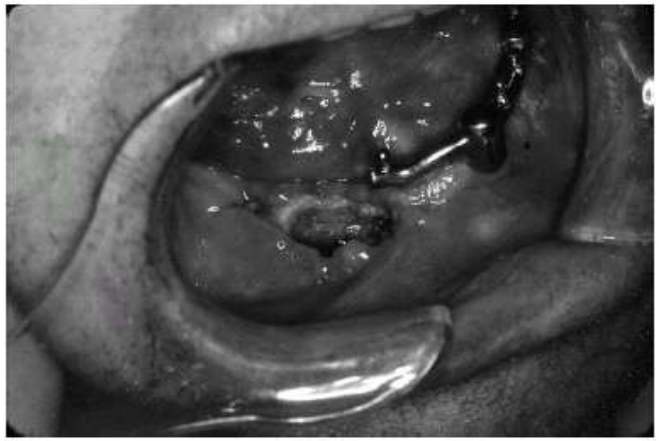


FIGURE 2. Exposed necrotic bone in the maxilla in a patient who was taking pamidronate (Aredia). Exposed bone occurred spontaneously.

Marx (Miami University) J Oral Max Surg Sept 2003

36 cases (24 Pamidronate, 6 Zoledronate, 6 both)(86% mandib)

Fig 1. Bone necrosis of the mandible on a female patient with metastatic breast cancer to bone under treatment with zoledronic acid.

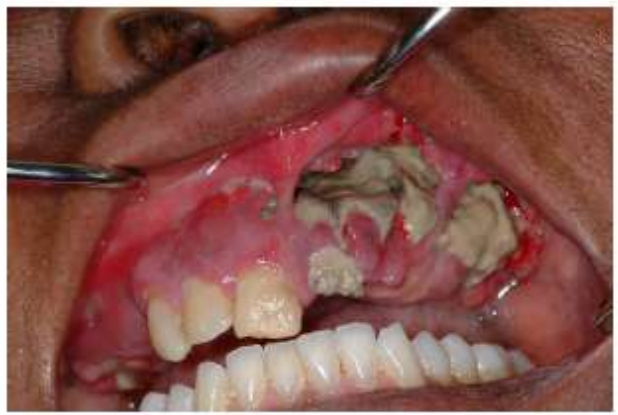
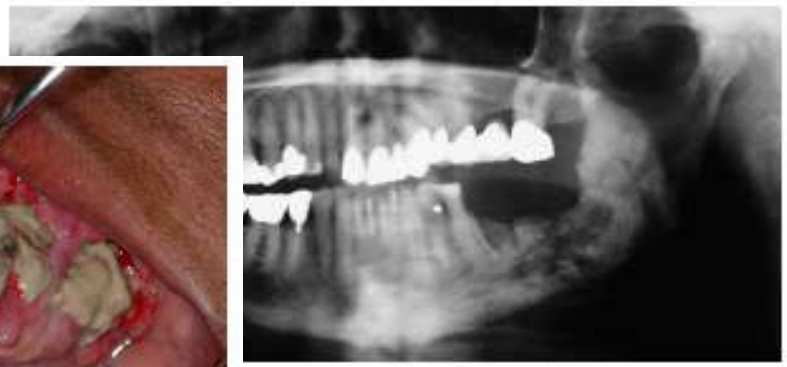


FIGURE 1. Exposed necrotic maxillary bone in a patient receiving zolendronic acid for 6 months. The patient had posterior maxillary extractions performed 4 months earlier. (Courtesy of Dr Jay Neugarten, New Hyde Park, NY.)



mic radiograph of the mandible following extrac-
teeth in a patient receiving pamidronate. The
tled bone in the region of the nonhealing extrac-

Migliorati, JCO 2003

5 cases

Ruggiero et al (Long Island) JOMS May'04

63 cases (56 pam/zol, 7 oral BPs)

ONJ (osteonecrosis of jaws)

" GRANDE

E' IL DISORDINE

SOTTO IL CIELO… "

Mikhael et al, JCO May 2019

ASCO special article abstract

Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

Joseph Mikhael, MD[1,2]; Nofisat Ismaila, MD[3]; Matthew C. Cheung, MD, SM[4]; Caitlin Costello, MD[5]; Madhav V. Dhodapkar, MD[6]; Shaji Kumar, MD[7]; Martha Lacy, MD[7]; Brea Lipe, MD[8]; Richard F. Little, MD[9]; Anna Nikonova, MD, CM[10]; James Omel, MD[11]; Namrata Peswani, MD[12]; Anca Prica, MD[13]; Noopur Raje, MD[14]; Rahul Seth, DO[15]; David H. Vesole, MD, PhD[16,17]; Irwin Walker, MBBS[18]; Alexander Whitley, MD, PhD[19]; Tanya M. Wildes, MD[20]; Sandy W. Wong, MD[21]; and Tom Martin, MD[21]

PURPOSE To provide evidence-based recommendations on the treatment of multiple myeloma to practicing physicians and others.

METHODS ASCO and Cancer Care Ontario convened an Expert Panel of medical oncology, surgery, radiation oncology, and advocacy experts to conduct a literature search, which included systematic reviews, meta-analyses, randomized controlled trials, and some phase II studies published from 2005 through 2018. Outcomes of interest included survival, progression-free survival, response rate, and quality of life. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations.

RESULTS The literature search identified 124 relevant studies to inform the evidence base for this guideline.

RECOMMENDATIONS Evidence-based recommendations were developed for patients with multiple myeloma who are transplantation eligible and those who are ineligible and for patients with relapsed or refractory disease.

Additional information is available at www.asco.org/hematologic-malignancies-guidelines.

J Clin Oncol 37:1228-1263.

Anderson et al JCO Mar 2018

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Role of Bone-Modifying Agents in Multiple Myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update

Kenneth Anderson, Nofisat Ismaila, Patrick J. Flynn, Susan Halabi, Sundar Jagannath, Mohammed S. Ogaily, Jim Omel, Noopur Raje, G. David Roodman, Gary C. Yee, and Robert A. Kyle

For patients with active symptomatic multiple myeloma that requires systemic therapy with or without evidence of lytic destruction of bone or compression fracture of the spine from osteopenia on plain radiograph(s) or other imaging studies, intravenous administration of pamidronate 90 mg over at least 2 hours or zoledronic acid 4 mg over at least 15 minutes every 3 to 4 weeks is recommended. Denosumab has shown to be noninferior to zoledronic acid for the prevention of skeletal-related events and provides an alternative. Fewer adverse events related to renal toxicity have been noted with denosumab compared with zoledronic acid and may be preferred in this setting. The update panel recommends that clinicians consider reducing the initial pamidronate dose

severe renal impairment and is not recommended in this setting. The update panel suggests that bone-modifying treatment continue for up to 2 years. Less frequent dosing has been evaluated and should be considered in patients with responsive or stable disease. Continuous use is at the discretion of the treating physician and the risk of ongoing skeletal morbidity. Retreatment should be

initiated at the time of disease relapse. The update panel discusses measures regarding osteonecrosis of the jaw. Additional information is available at www.asco.org/hematologic-malignancies-guidelines and www.asco.org/guidelineswiki.

Anderson et al JCO Mar 2018

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Role of Bone-Modifying Agents in Multiple Myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update

Kenneth Anderson, Nofisat Ismaila, Patrick J. Flynn, Susan Halabi, Sundar Jagannath, Mohammed S. Ogaily, Jim Omel, Noopur Raje, G. David Roodman, Gary C. Yee, and Robert A. Kyle

ONJ

ONJ is a major complication that is increasingly observed when more potent bisphosphonates, such as pamidronate and zoledronic acid, have been used. Although first described with bisphosphonates, ONJ also occurs with denosumab. The Expert Panel agrees with the recommendations described in the revised FDA label for zoledronic acid and pamidronate, Dear Doctor letters, a white paper, and various position papers or statements. All patients with cancer should receive a comprehensive dental examination and appropriate preventive dentistry before bone-modifying therapy. Active oral infections should be treated, and sites that are at high risk for infection should be eliminated. While on therapy, patients should maintain excellent oral hygiene and avoid invasive dental procedures, if possible. Continuation of a bone-targeting agent in the setting of ONJ has to be individualized and dependent on a risk–benefit ratio and the severity of bone disease. Other notable complications of BMAs include atypical fractures of the femur.[19]

Raje et al, Lancet Oncol Mar 2018

Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study

Mhaskar et al Cochrane Database Syst Rev 2017

Cochrane Library

Cochrane Database of Systematic Reviews

Bisphosphonates in multiple myeloma: an updated network meta-analysis (Review)

Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B

Bisphosphonates may increase ONJ compared with placebo but the confidence interval is very wide (RR 4.61, 95% CI 0.99 to 21.35; P = 0.05; six studies; 1284 participants; low-quality evidence). The results from the network meta-analysis did not show any evidence for a difference in the incidence of ONJ (eight RCTs, 3746 participants) between bisphosphonates. Data from nine observational studies (1400 participants) reported an incidence of 5% to 51% with combination of pamidronate and zoledronate, 3% to 11% with zoledronate alone, and 0% to 18% with pamidronate alone.

Osteonecrosi dei mascellari

(osteonecrosis of jaws, ONJ)

da farmaci

(*bifosfonati, denosumab, altri*)

Osteoradionecrosi dei mascellari

(osteoradionecrosis of jaws, ORJ o ORNJ)

Osteomielite dei mascellari

Non esiste un nome codificato

Osteonecrosis of Jaw (Jaws) (ONJ)

Bisphosphonate-Related Osteonecrosis of Jaws (BRON) (BRONJ)

Chemo-osteonecrosis

Osteo (chemo) necrosis

Avascular necrosis ….

Bis-Phossy-jaw

Jaw avascular bone necrosis

Ecc. ecc

V.Fusco

Non esiste un nome codificato

Osteonecrosis of Jaw (Jaws) (ONJ)

Bisphosphonate-Related Osteonecrosis of Jaws (BRON) (BRONJ)

Ch

Ava

Jaw

Ecc

ARONJ = Antiresorptive-Related ONJ

is

DRONJ : Drug-Related ONJ

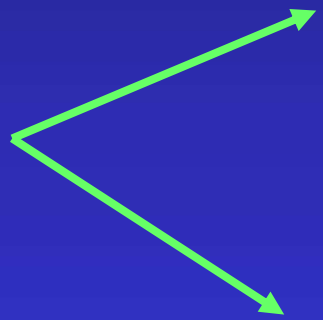
MRONJ = Medication-Related ONJ

ONJ

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

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)

Ministero del Lavoro, della Salute e delle Politiche sociali

DIPARTIMENTO DELLA QUALITÀ
DIREZIONE GENERALE DELLA PROGRAMMAZIONE SANITARIA, DEI LIVELLI DI ASSISTENZA E DEI PRINCIPI ETICI DI SISTEMA
UFFICIO III

RACCOMANDAZIONE PER LA PREVENZIONE DELL'OSTEONECROSI DELLA MASCELLA/MANDIBOLA DA BIFOSFONATI

I bifosfonati possono essere causa di osteonecrosi a carico della mascella/mandibola

L'osteonecrosi della mascella/mandibola da bifosfonati è una patologia ancora in fase di approfondimento. I dati riportati dalla letteratura scientifica nazionale ed internazionale indicano un incremento dei casi nell'ultimo decennio. E' necessario, pertanto, adottare tutte le misure idonee per prevenire e minimizzare tale effetto indesiderato. La presente Raccomandazione, rivolta a tutti gli operatori sanitari, si pone come supporto alla corretta gestione dei pazienti che necessitano di cure odontoiatriche e che hanno assunto, stanno assumendo o dovranno assumere bifosfonati in ambito oncologico.

Raccomandazione n. 10, settembre 2009

CORRESPONDENCE

Osteonecrosis of the Jaw and Bisphosphonates

TO THE EDITOR: Cases of osteonecrosis of the jaw in connection with the use of bisphosphonates were reported in 2003.[1,2] In 2004, the International Myeloma Foundation conducted a Web-based survey to assess the risk factors for osteonecrosis of the jaw. Of 1203 respondents, 904 had myeloma and 299 breast cancer. Both osteonecrosis and suspicious findings, including bone erosions and spurs plus exposed bone, were assessed. Sixty-two patients with myeloma had osteonecrosis of the jaw and 54 had suspicious findings; 13 patients with breast cancer had osteonecrosis and 23 had suspicious findings — a total of 152 patients with either osteonecrosis or suspicious findings. Of the patients with myeloma, 71 percent had received zoledronic acid and 29 percent had received only pamidronate.

Figure 1 displays the cumulative incidence of

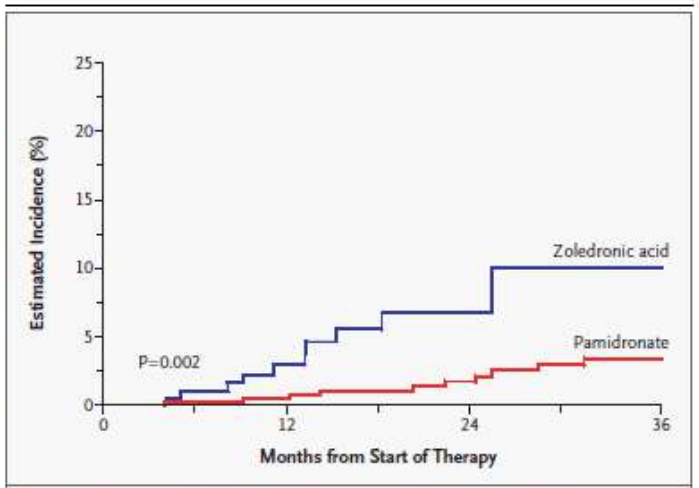


Figure 1. Time to the Onset of Osteonecrosis of the Jaw in Patients with Myeloma Receiving Zoledronic Acid or Pamidronate.

Brian G.M. Durie, M.D.
Cedars–Sinai Outpatient Cancer Center
Los Angeles, CA 90048-1804
bdurie@salick.com
Michael Katz, M.B.A.
International Myeloma Foundation
North Hollywood, CA 91607-3421
John Crowley, Ph.D.
Cancer Research and Biostatistics
Seattle, WA 98101-1468

N ENGL J MED 353;1 WWW.NEJM.ORG JULY 7, 2005

International Myeloma Foundation – Web Survey

International Myeloma Foundation – Web Survey

Michael Katz

Brian Durie

Consumer Groups Look To Improve Adverse Event Reporting Systems

Journal of the National Cancer Institute, Vol. 97, No. 24, December 21, 2005

BRONJ Case Definition

To distinguish BRONJ from other delayed healing conditions, the following working definition of BRONJ has been adopted by the AAOMS:

Patients may be considered to have BRONJ if all of the following three characteristics are present:

1. *Current or previous treatment with a bisphosphonate;*
2. *Exposed bone in the maxillofacial region that has persisted for more than eight weeks; and*
3. *No history of radiation therapy to the jaws.*

It is important to understand that patients at risk for BRONJ or with established BRONJ can also present with other common clinical conditions not to be confused with BRONJ. Commonly misdiagnosed conditions may include, but are not limited to, alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology and TMJ disorders.

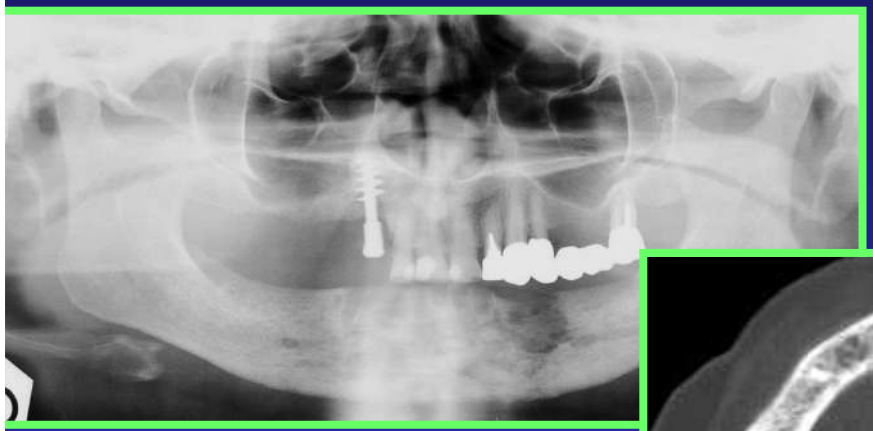
AAOMS 2006

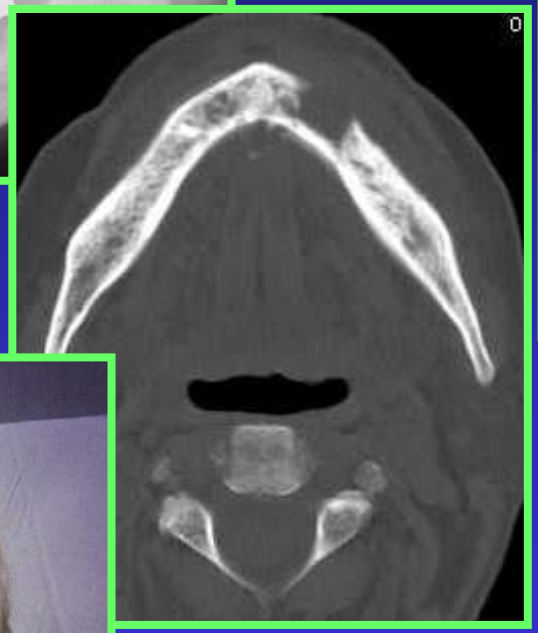
Una definizione "*restrittiva*" (necessaria…?)

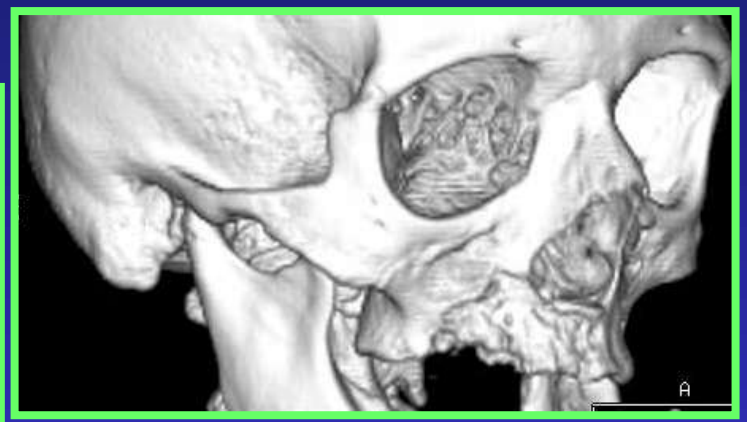
Primi anni : casi radiotrattati (creduti localizzazioni di malattia)

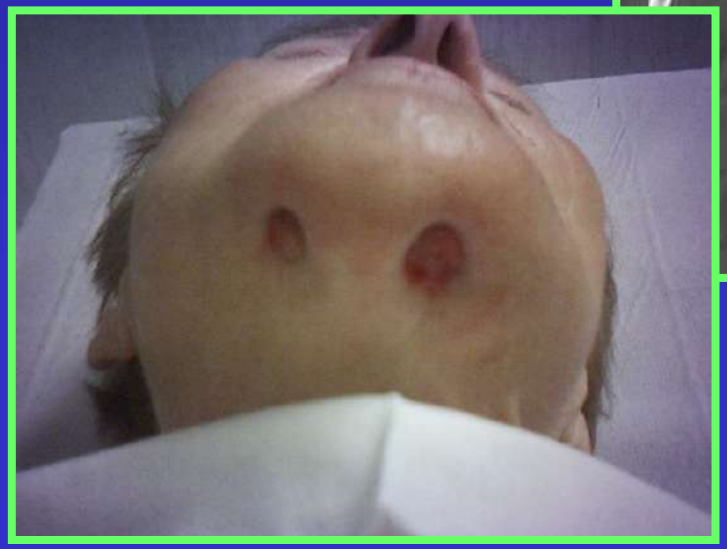
Ma esistono casi con comparsa tardiva di "osso esposto"
o senza osso esposto ma con fistole, fratture, ecc. ***(Bagan 2008)***

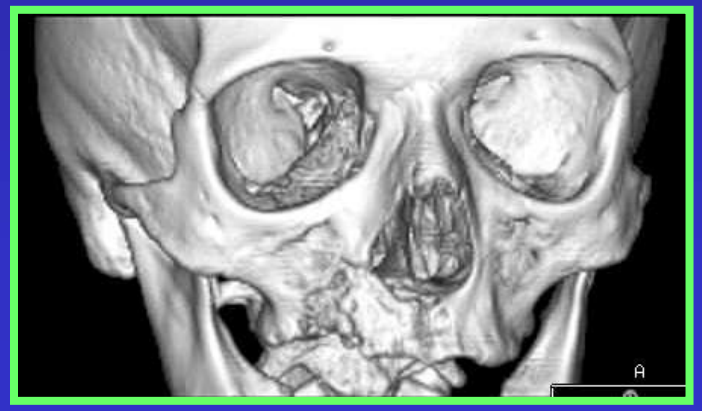
ASO Alessandria 2005



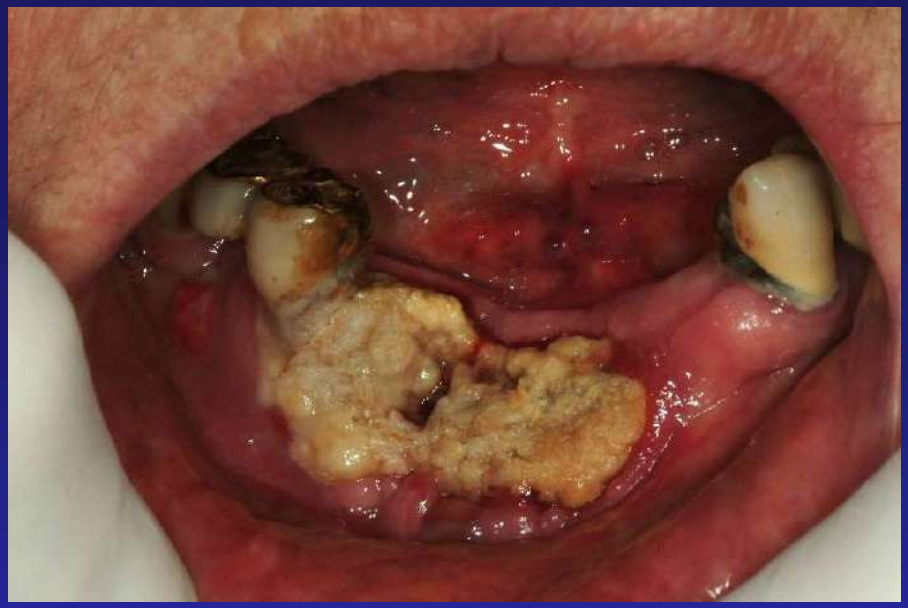


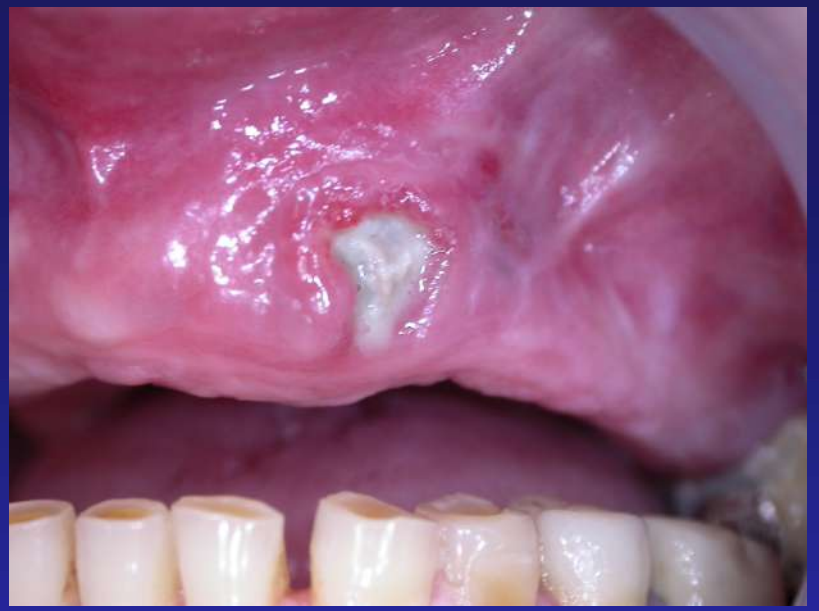


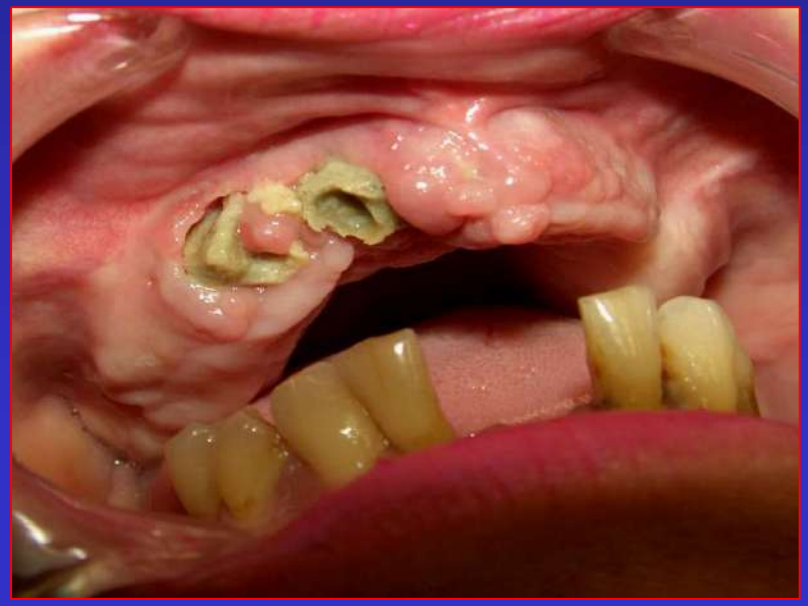




V.Fusco-P.Russo

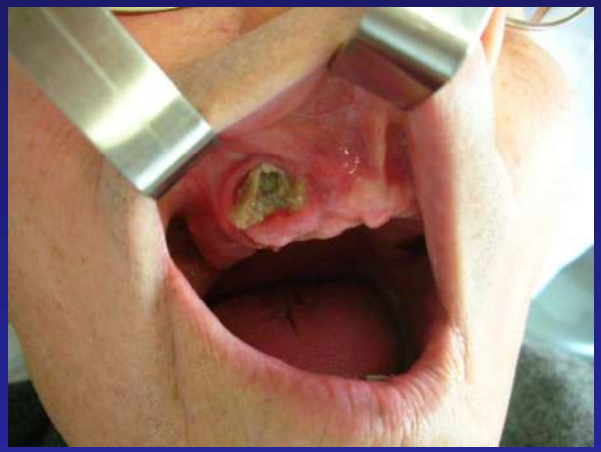






Casi del Gruppo ONJ della Rete Oncologica Piemonte-VdA

ONJ correlata ai bifosfonati



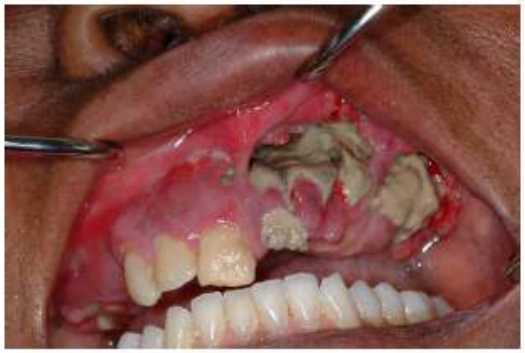
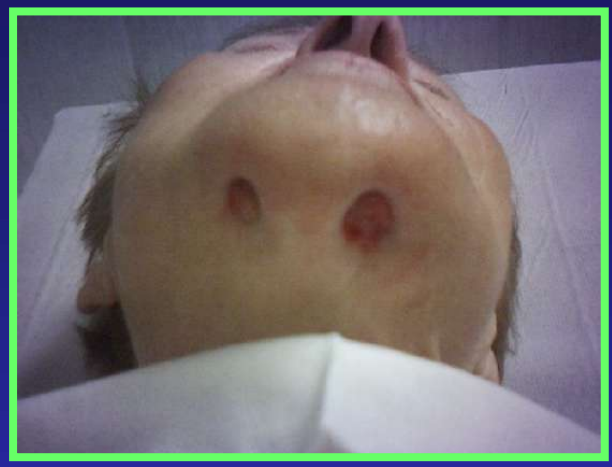


FIGURE 1. Exposed necrotic maxillary bone in a patient receiving zolendronic acid for 6 months. The patient had posterior maxillary extractions performed 4 months earlier. (Courtesy of Dr Jay Neugarten, New Hyde Park, NY.)



Ampia variabilità in

-modalità di esordio (durante e dopo BP)

-sintomaticità (dolore, infezioni, ecc.)

-decorso clinico (spontaneo / dopo terapia)

SINTOMI E SEGNI

- Osso esposto necrotico, ulcerazioni gengivali, ecc. (anche linguali, *Treuter 2008*)
- Dolore
- Difficoltà alla masticazione, deglutizione, fonazione
- Fetor ex oris
- Tumefazioni, ascessi
- Fistole orocutanee, fratture mandibolari, ecc.
- Fistole oronasali; fistole sottorbitarie

Non sempre sintomi correlati alla gravità del quadro clinico…

- Dolore (non sempre presente; spesso da lesioni piccole…)
- Fetor ex oris (invalidante per la socialità)

DECORSO CLINICO VARIABILE

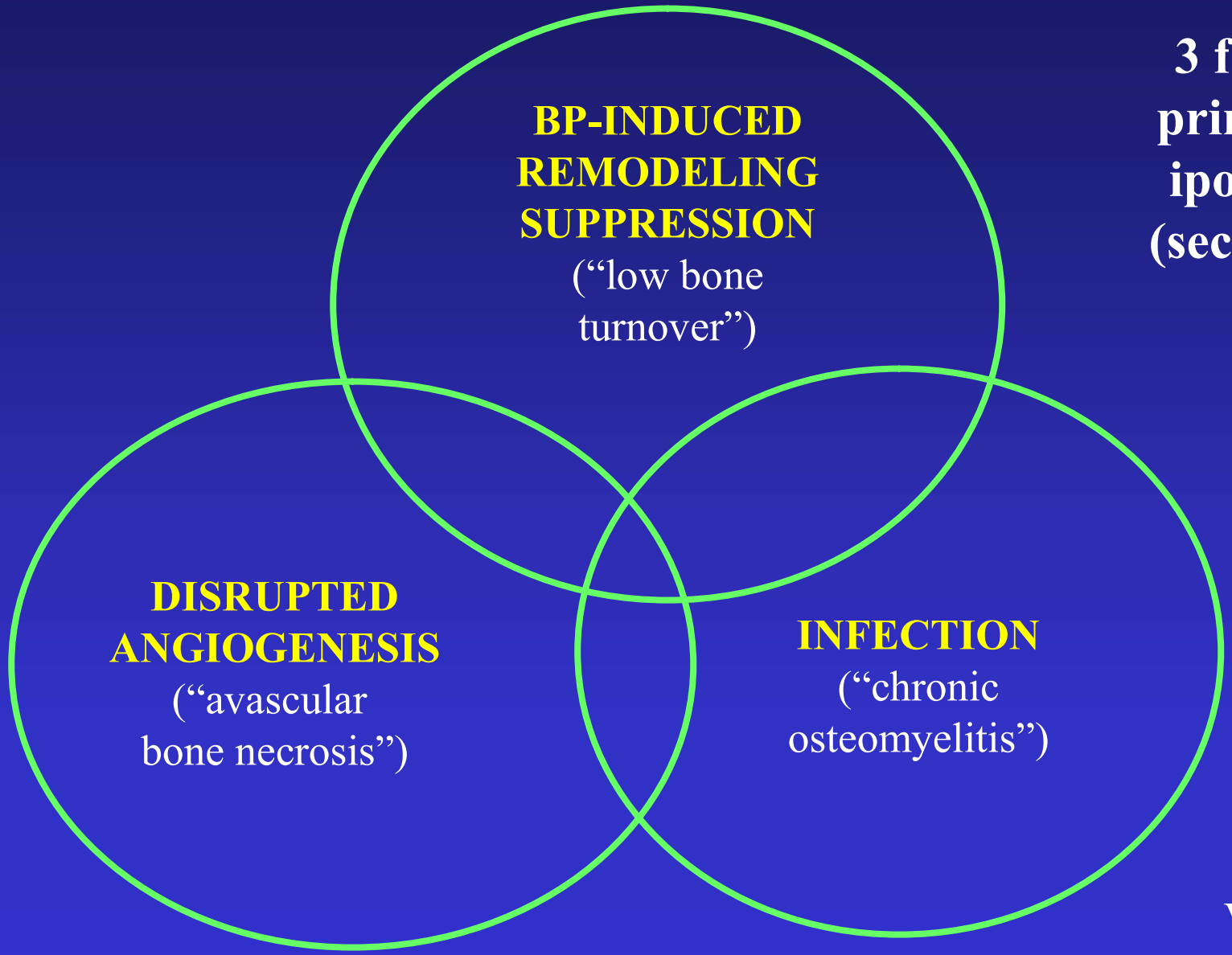
- Talvolta indolente
- Talvolta intermittente (fasi di remissione / stabilità)
- Talvolta aggressivo (anche multicentrico… !!)

Dipende da:

- ritardo nella diagnosi ?
- tipo di BP ? (es. BP orali → più benigno)
- altri fattori individuali ?

Yarom 2007, Vescovi 2007, ecc

BR-ONJ : IPOTESI ETIOPATOGENETICHE

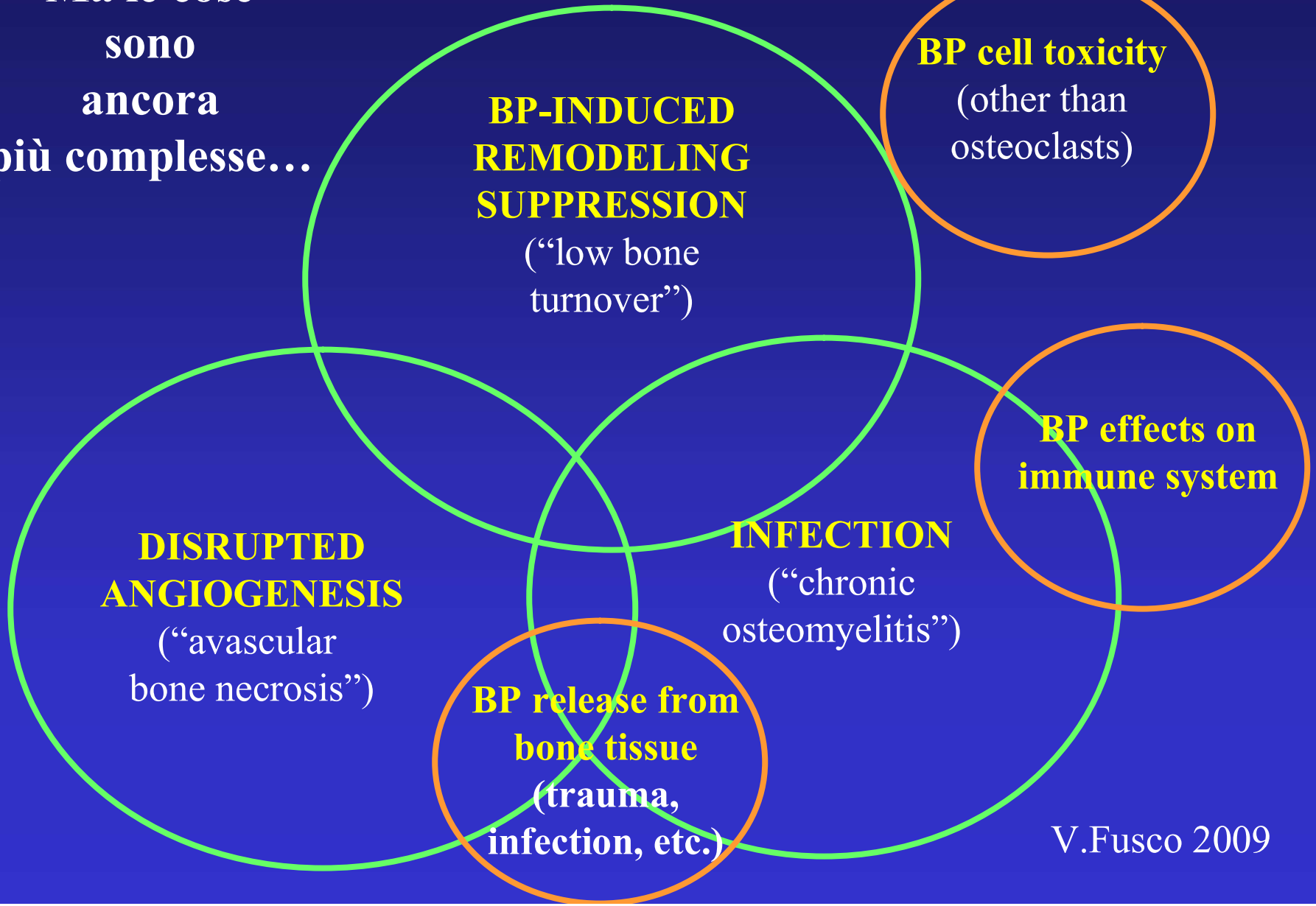


3 fattori principali ipotizzati (sec. Allen)

V.Fusco

ONJ : IPOTESI ETIOPATOGENETICHE

Ma le cose sono ancora più complesse…



V.Fusco 2009

Tecniche di IMAGING

-**Rx OPT** Poco sensibile e specifica, ma ineludibile (1° livello)

-**Scintigrafia ossea** Molto sensibile, poco specifica (Chiandussi 2006, Zanglis 2008)

-**TC** Quadri nosografici variabili (Bianchi 2007, Raje 2008, Maksimovic 2008, ecc.)

-**"Cone beam CT"** In aumento (bassa dosse di esposizione) (Kumar 2007)

-**Risonanza Magnetica**

Utile per programmare terapia chirurgica maggiore ? (Bedogni 2007, Bisdas 2008, Wutzl 2006, ecc.)

Capace di individuare lesioni pre-cliniche ? (Garcia-Ferrer 2008)

-**Med.Nucleare (sestamibi; FDG-PET; NaF-PET, ecc)** ? (Catalano 2007, Raje 2008, Ho 2008)

Staging and Treatment Strategies (See Table 1)

Staging

In order to direct rational treatment guidelines and collect data to assess the prognosis in patients who have used either IV or oral bisphosphonates, the AAOMS proposes use of the following staging categories:

1. Patients at risk: No apparent exposed/necrotic bone in patients who have been treated with either IV or oral bisphosphonates.

2. Patients with BRONJ
   Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection.
   Stage 2: Exposed/necrotic bone in patients with pain and clinical evidence of infection.
   Stage 3: Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border

AAOMS Position Paper 2006 (JOMS 2007)

Lo stadio cambia ….

Es. Esperienza di Parma (Vescovi, Merigo, Manfredi): Laser Terapia e/o chirurgia

-“stabilizzazioni “

-“risoluzioni”

→ a lungo termine (“*stadio 0*”)

→ intermittenti

-”progressioni”

e se cambia anche la definizione..

Proposta di Bagan, includente casi senza osso esposto

(Bagan, Oral Oncol 2008)

V.Fusco

SENZA OSSO ESPOSTO

Alterazioni ossee senza (ancora) osso esposto

Non necessariamente in stadio “iniziale”

Necessità di studio con TC !?!

V.Fusco

AAOMS : Stadio 0 ….

Alterazioni ossee senza (ancora) osso esposto

o allargamento della definizione ?

Colella G, Campisi G, Fusco V

AAOMS position paper : BP-related ONJ 2009 update: The need to refine the BRONJ definition

JOMS (J Oral Max Surg) may 2009

V.Fusco

Osteonecrosi mandibolare e mascellare in pazienti in terapia con bifosfonati (BP) :

Quali "fattori di rischio" ?

Studio delle caratteristiche dei casi osservati :

- **tipo e durata del trattamento con BP,**
- **storia odontoiatrica,**
- **trattamenti oncologici e di supporto,**
- **abitudini (fumo, alcool, ecc)**
- **caratt. anagrafiche (sesso, età)**

e confronto con la popolazione generale (dei trattati con BP ma senza ONJ) …

V.Fusco

ONJ : Quali "fattori di rischio" ?

Risultati discordanti in letteratura :

- **storia odontoiatrica (estraz, traumi, ecc)** +++
- **tipo e durata del trattamento con BP** +++
- **trattamenti oncologici e di supporto (steroidi, antiangiogenetici, ecc)** +/-
- **abitudini (fumo, alcool, ecc)** +/-
- **caratt. anagrafiche (sesso, età)** +/-
- **diabete** +/-

V.Fusco

Progetto Trasversale di Rete

Studio caso-controllo sui fattori di rischio nell'insorgenza di osteonecrosi mandibolare in pazienti oncologici trattati con difosfonati

Coordinamento : SOC Oncologia, Alessandria

Elaborazione dati: CPO Piemonte

Rischio di ONJ : il tipo di BP

In ordine decrescente :

Zoledronato > P+Z > Pamidronato >> BP os

(Ibandronato ??)

Durie 2005

Bamias 2005

Badros 2006

Hoff 2008

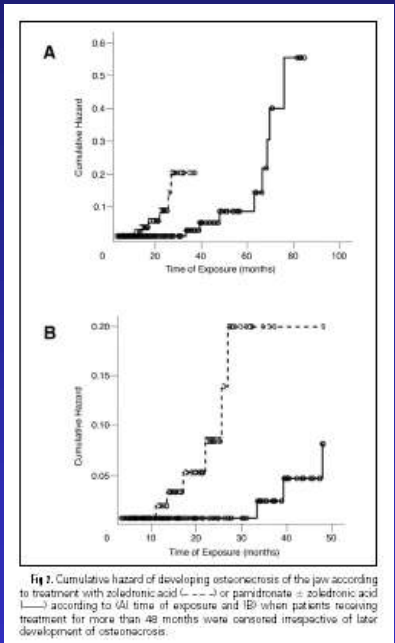


Fig 2. Cumulative hazard of developing osteonecrosis of the jaw according to treatment with zoledronic acid (– – –) or pamidronate ± zoledronic acid (——) according to (A) time of exposure and (B) when patients receiving treatment for more than 48 months were censored irrespective of later development of osteonecrosis.

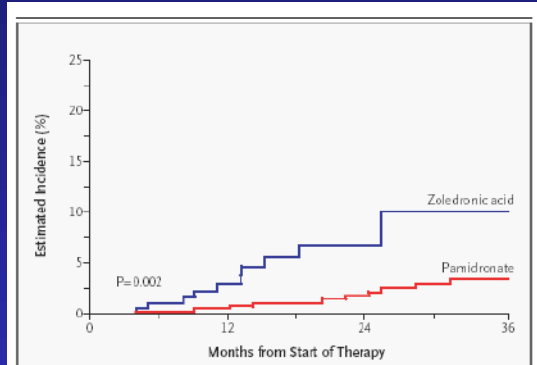
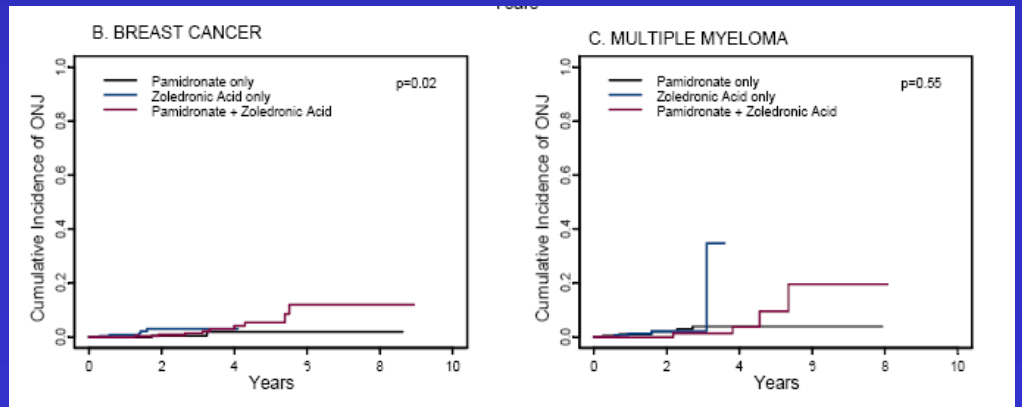


Figure 1. **Time to the Onset of Osteonecrosis of the Jaw in Patients with Myeloma Receiving Zoledronic Acid or Pamidronate.**

Among patients receiving zoledronic acid, the occurrence of osteonecrosis of the jaw is particularly notable at months 4, 8, 9, 11, 13, 15, and 18. With data censored at 36 months, the estimated incidence among patients receiving zoledronic acid was 10 percent and that among those receiving pamidronate was 4 percent. Without censoring, the mean time to the onset of osteonecrosis among patients receiving zoledronic acid was 18 months, as compared with 6 years for patients receiving pamidronate (P=0.002).



ONJ

Mediana di comparsa :
(mesi, o numero
di somministrazioni…)

9-18 mesi per Zoledronato
12-48 mesi per Pamidronato
intermedia per Pam → Zol

ma ... **RANGE !!!** : da pochi mesi (poche somm) a molti anni

→ rischio compare da subito !
→ rischio persiste per anni (anche dopo fine terapia..)
→ importanza di evento scatenante (estraz, protesi)
→ importanti fattori individuali (genetici?
endocrinologici?)

Pazienti con ONJ ricevevano in media più infusioni di non-ONJ…

Effetto della lunga sopravvivenza ?

(mieloma, ca mammella, ca prostata > ca polmone > altri)

ONJ : PREVENZIONE

Due possibilità :

A) agire sui fattori di rischio odontoiatrici

B) ottimizzare il trattamento con BP
per migliorare il rapporto costo-benefici

V.Fusco

ONJ : RACCOMANDAZIONI (dal 2004-2005) DI MISURE "PREVENTIVE"

- screening nei pazienti già in trattamento (valutazione odontoiatrica; non estrazioni e terapie aggressive)
- attenta valutazione dei pazienti candidati a bifosfonati e bonifica pre-terapia

Practical Guidelines for the Prevention, Diagnosis, and Treatment of Osteonecrosis of the Jaw in Patients With Cancer

By Salvatore Ruggiero, DMD, MD, Julie Gralow, MD, Robert E. Marx, DDS, Ana O. Hoff, MD, Mark M. Schubert, DDS, MDS, Joseph M. Huryn, DDS, Bela Toth, DDS, MS, Kathryn Damato, RDH, MS, CCRP, and Vicente Valero, MD, FACP

Long Island Jewish Medical Center, New Hyde Park; Memorial Sloan-Kettering Cancer Center, New York, NY; University of Washington Medical Center; Seattle Cancer Care Alliance, Seattle, WA; University of Miami School of Medicine, Miami, FL; The University of Texas M.D. Anderson Cancer Center, Houston, TX; and University of Connecticut Health Center, Farmington, CT

Journal Practice Oncology, January 2006

Indicazioni per pazienti candidati a terapia con bifosfonati

- Visita odontoiatrica + Rx Ortopantomografia basale
- Bonifica dentaria e attesa della guarigione
- Verifica delle protesi esistenti
- Educazione : all'igiene orale , alla sorveglianza del cavo orale, alla segnalazione precoce delle lesioni e sintomi, evitare procedure odonto non conservative.
- Controlli specialistici periodici

A.Baraldi , V.Fusco

original article

Annals of Oncology
doi:10.1093/annonc/mdn526

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

C. I. Ripamonti[1]*, M. Maniezzo[2], T. Campa[1], E. Fagnoni[1], C. Brunelli[1], G. Saibene[3], C. Bareggi[1], L. Ascani[3] & E. Cislaghi[2]

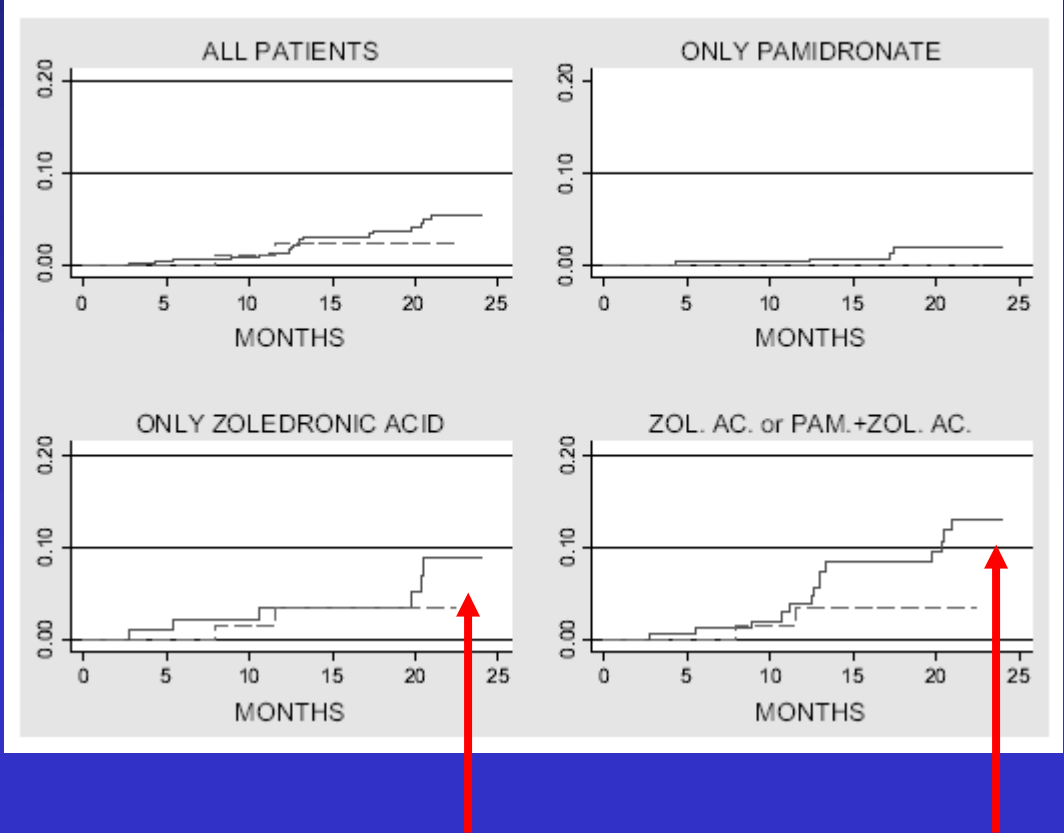
[1]*Palliative Care Unit (Pain Therapy and Rehabilitation);* [2]*Consultant Dental Team;* [3]*Hospital Pharmacy, IRCCS Foundation, National Cancer Institute of Milan, Milan, Italy*

Received 15 February 2008; revised 17 June 2008; accepted 23 June 2008

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.

Ripamonti , Ann Oncol 2009

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).



Rischio di ONJ a 2 anni (in PRE-Group) ≥ 10% dopo Zoledronato

ridotto con misure di prevenzione

Ripamonti, Ann Oncol 2009

original article

Annals of Oncology
doi:10.1093/annonc/mdn554

Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid

M. A. Dimopoulos[1]*, E. Kastritis[1], C. Bamia[2], I. Melakopoulos[3], D. Gika[1], M. Roussou[1], M. Migkou[1], E. Eleftherakis-Papaiakovou[1], D. Christoulas[1], E. Terpos[4] & A. Bamias[1]

[1]*Department of Clinical Therapeutics;* [2]*Department of Hygiene and Epidemiology, Medical School, University of Athens;* [3]*Department of Maxillofascial Surgery, H. Dunant Hospital;* [4]*Department of Biomedical Research, 251 General Air Force Hospital, Athens, Greece*

Received 6 February 2008; revised 13 June 2008; accepted 15 July 2008

Patients and methods: Patients with MM who received zoledronic acid were included in this analysis. Patients with a previous use of other bisphosphonates were excluded; patients were stratified into group A (n = 38) and group B (n = 90) if treatment was started before or after the implementation of preventive measures.

128 paz, solo mieloma (38 senza e 97 con misure preventive)

solo Zoledronato

Dimopoulos , Ann Oncol 2009

Problema :

Le misure di prevenzione della ONJ COSTANO

-in termini economici
-in termini di organizzazione del lavoro
-in termini di tempo

e sono di più difficile attuazione

NEI CENTRI MEDI E PICCOLI

rispetto ai grandi centri ed alle sedi universitarie

BPs : Optimising the risk/benefit ratio

- When compared to other cancer therapies, the frequency and severity of adverse events of BPs are mild and infrequent.

- Evidence-based criteria are needed to determine when the BPs should be started and stopped… (→ empirical recommendations based on disease type, life expectancy of the patient, SRE risk, and the ease to receive treatment).

- The cost effectiveness of routine long-term treatment has been questioned (McKeage, *Pharmacoeconomics* 2008).

- Small but finite risk of toxicity.

→ A MORE SELECTIVE USE OF BISPHOSPHONATES WOULD BE APPRIOPRIATE

Coleman RE, Br J Cancer 2008

2006-2007 : new guidelines and recommendations

Mayo Clinic Consensus Statement for the Use of Bisphosphonates in Multiple Myeloma

Lacy, Mayo Clin Proc 2006

Pamidronate and Zoledronic acid are equally active.
Pamidronate is favored (ONJ).
After 2 years : discontinuing or continuing every 3 months.

American Society of Clinical Oncology 2007 Clinical Practice Guideline Update on the Role of Bisphosphonates in Multiple Myeloma

Robert A. Kyle, Gary C. Yee, Mark R. Somerfield, Patrick J. Flynn, Susan Halabi, Sundar Jagannath, Robert Z. Orlowski, David G. Roodman, Patricia Twilde, and Kenneth Anderson

Kyle, Journal Clinical Oncology 2007

Pamidronate 90 mg or Zoledronic acid 4 mg q 3-4 Wks (or Clodronate)
For 2 years (then : consider discontinuing in patients with responsive or stable disease)

2006-2007 : new guidelines and recommendations

Use of Bisphosphonates in Multiple Myeloma: IMWG Response to Mayo Clinic Consensus Statement

Durie, Mayo Clin Proc 2007

BP for 1 year (for pts with Complete Response or a very good Partial Response) or 2 years (for less good response or active disease). Pamidronate is favored over zoledronic acid.

The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Multiple Myeloma: A Clinical Practice Guideline

K. Imrie, A. Stevens, J. Makarski, R. Esmail, J. Meharchand, R. Meyer, and the members of the Hematology Disease Site Group

Imrie et al, Cancer Care Ontario Program 2007

Clodronate or Pamidronate or Zoledronic Acid for a minimum of 2 years . Clodronate and pamidronate might be the preferred agents.

2008: new guidelines and recommendations

Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel

Aapro M. et al, Annals of Oncology mar 2008

Since the risk of SREs is continuous, the expert panel recommends continuing treatment until 2 years, even if a patient experiences a bone event. Continuation of therapy beyond 2 years based on an individual risk assessment is recommended.

- Before starting N-BP treatment, patients should have a dental examination and appropriate treatment and should be advised to maintain good oral hygiene.
- For each patient with ONJ, an individual benefit/risk evaluation should be carried out to assess continuation or temporary discontinuation of BP therapy.

Myeloma : European recommendations

The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network

E. Terpos[1,2*], O. Sezer[3], P. I. Croucher[4], R. García-Sanz[5], M. Boccadoro[6], J. San Miguel[5], J. Ashcroft[7], J. Bladé[8,9], M. Cavo[10], M. Delforge[11], M.-A. Dimopoulos[1], T. Facon[12], M. Macro[13], A. Waage[14] & P. Sonneveld[15]

Annals of Oncology Advance Access published May 22, 2009

Results: The panel recommends the use of BPs in MM patients suffering from lytic bone disease or severe osteoporosis. Intravenous administration may be preferable; however, oral administration can be considered for patients unable to make hospital visits. Dosing should follow approved indications with adjustments if necessary. In general, BPs are well tolerated, but preventive steps should be taken to avoid renal impairment and osteonecrosis of the jaw (ONJ). The panel agrees that BPs should be given for 2 years, but this may be extended if there is evidence of active myeloma bone disease. Initial therapy of ONJ should include discontinuation of BPs until healing occurs. BPs should be restarted if there is disease progression.

Conclusions: BPs are an essential component of MM therapy for minimizing skeletal morbidity. Recent retrospective data indicate that a modified dosing regimen and preventive measures can greatly reduce the incidence of ONJ.

ONJ : quanto è frequente ?

INCIDENZA : ?

PREVALENZA : ?

“FREQUENZA” : ?

tra <0.5% e >12%

Numeri assoluti : ?

(epidemiologia; carichi di lavoro…)

Rischio individuale : ?

(rischio nel tempo…; costi-benefici)

EPIDEMIOLOGIA: ONJ DA BIFOSFONATI E ALTRI FARMACI

Quali sono i farmaci che possono determinare la ONJ?

Quali sono le categorie di pazienti a maggior rischio di ONJ?

Esistono ad oggi "nuovi" sottogruppi di popolazione a più alto rischio?

FONTI DI DATI EPIDEMIOLOGICI

- ✓ **Studi randomizzati** (bracci con/senza farmaci in studio)
- ✓ **Studi osservazionali, case series** (bias di selezione…)
- ✓ **Studi sistematici di popolazione** (registro tumori, ecc)
- ✓ **Studi retrospettivi su database** (assicurazioni, dimissioni ospedaliere, utenti sistema sanitario)
- ✓ **Surveys di specialisti o unità specialistiche** (odonto / maxillofacciali) **o di centri/gruppi oncologici** (es. Rete Oncologica Piemonte –VdA)

EPIDEMIOLOGIA: ONJ DA BIFOSFONATI E ALTRI FARMACI

Pazienti oncologici

Zoledronato 0.3-1.1 %
Denosumab 0.7-1.9%
Bevacizumab 0.2%
Beva+Zoled. 0.9%

Pazienti osteoporotici

BP orali 0.004-0.1%

(Placebo 0-0.020%)

Dati da trials :

SOTTOSTIMA !

da Ruggiero, JOMS 2014 - modif

INTERDISCIPLINARIETA' !!!

Oncologia

25 centri

Ematologia

15 centri

Chir. Maxillo Facciale

Odontoiatria

19 centri

ONJ in Piemonte –Valle d'Aosta (update: dicembre 2008)

247 casi segnalati

20 casi : pazienti non oncologici
6 casi : pazienti oncologici non residenti in Piem-VdA
21 casi : pazienti con dati incompleti sui BP

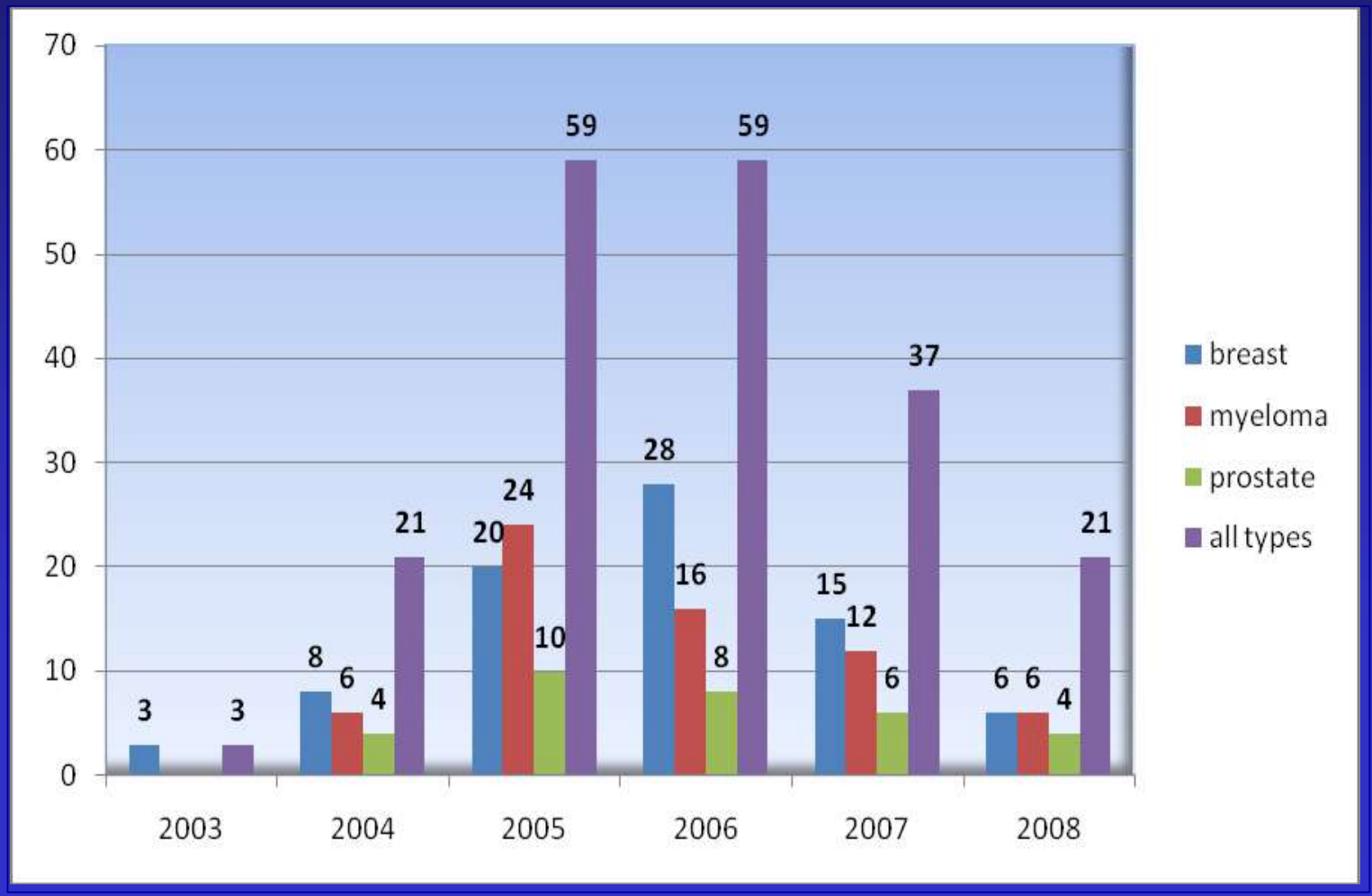
200 casi con dati completi sul trattamento con BP

178	**(89%)**	**acido zoledronico**
64	**(32%)**	**pamidronato**
4	**(2%)**	**ibandronato**
4	**(2%)**	**alendronato**
1	**(0.5%)**	**clodronato**

identificati dopo un controllo incrociato riportato da centri di oncologia, ematologia medica e patologia orale

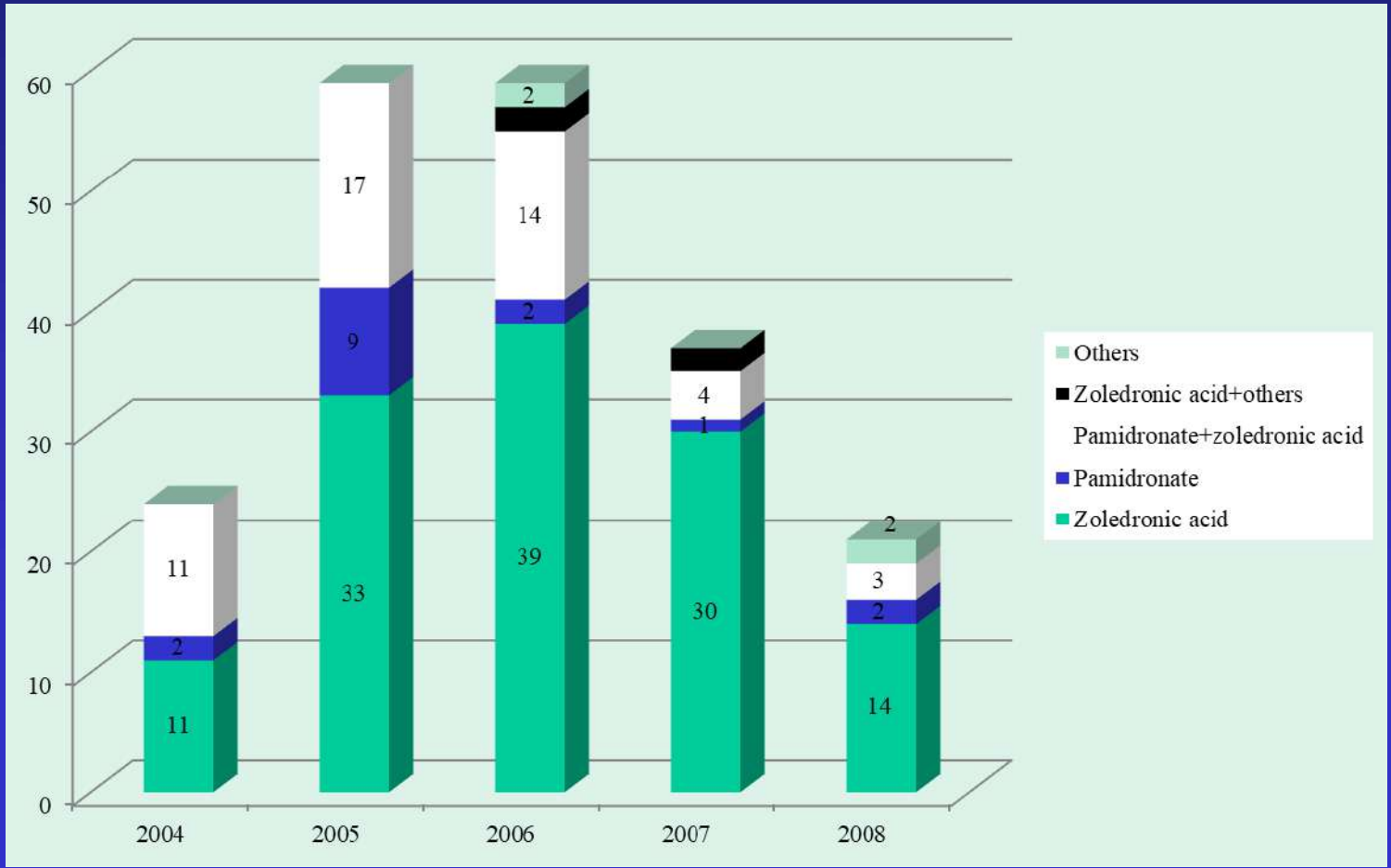
Risultati: variazione di incidenza (nuovi casi) negli anni

Il numero di nuovi casi per anno si è ridotto negli anni 2007 e 2008 (37 e 21, rispettivamente) in confronto agli anni 2005 e 2006 (59 e 59 casi per anno, rispettivamente).



Risultati: variazione di incidenza (nuovi casi) negli anni

Il numero di nuovi casi per anno si è ridotto negli anni 2007 e 2008 (37 e 21, rispettivamente) in confronto agli anni 2005 e 2006 (59 e 59 casi per anno, rispettivamente).



I nuovi casi di ONJ stanno diminuendo? Diminuiranno?

Forse SI perché :

- screening / prevenzione nei pazienti già in trattamento
  (valutazione odontoiatrica; non terapie aggressive)
- attenta valutazione dei pazienti candidati a bifosfonati…
- bifosfonati non prolungati oltre i 24 mesi…
- new switch (es Zoledronico → Pamidronato, Ibandronato, ecc)…

Forse NO perché :

- *apparente* "picco" di osservazioni nel 2004-2005 *("harvesting")*
- maggiore lunghezza di sopravvivenza (e follow-up)
  (nuovi farmaci, nuove tecnologie, terapie di supporto, ecc.)
- nuovi cofattori? (es thalidomide ed antiangiogenetici)….
- maggiore attenzione e consapevolezza
  (→ diagnosi in fase clinica iniziale)
- possibilità di diagnosi preclinica ? (scintigrafia ossea, RM,…)
- nuovi utilizzi dell'ac. zoledronico (CTIBL, osteoporosi)(adjuv ?)

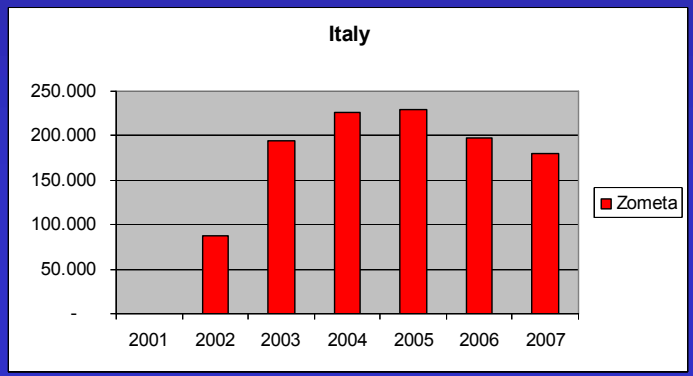
V.Fusco

Probabilmente
i nuovi casi di ONJ stanno diminuendo :

a) **Per la prevenzione dentaria (!!?)**
b) **Per la ridotta prescrizione di BP (?)**

220 casi di ONJ in Piemonte-VdA (popolazione: 4.3 Milioni)
In diminuzione !

Casi totali di ONJ in Italia (58 Milioni): 2000 –3000 ?
In diminuzione !?



Prescrizioni di Zometa in Italia

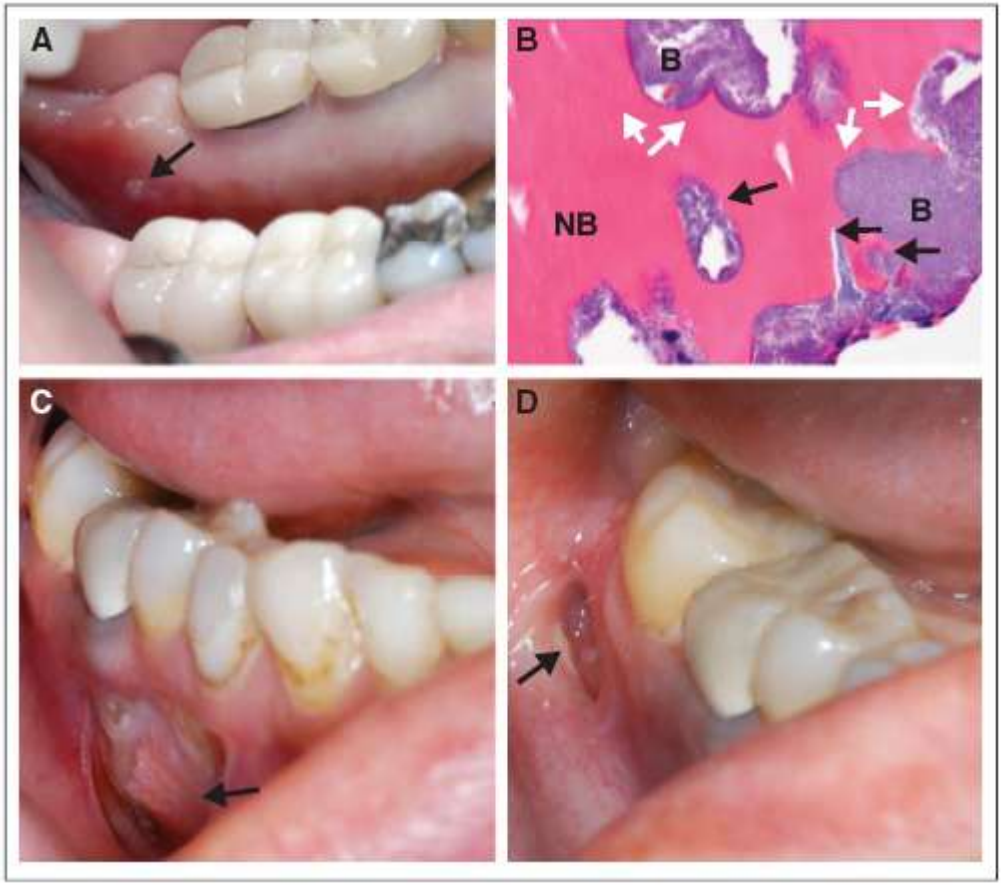
ONJ da Bevacizumab da solo (senza BP)

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

DENOSUMAB

- ECCO-ESMO Congress (Berlino, sett 2009)

- 2 studi randomizzati di non-inferiorità
  DENOSUMAB (sc) versus ZOMETA (ev) q28d

a) met. ossee da tumori della mammella (2046 pz)
b) MM + tumori diversi da mammella e prostata (1776 pz)

DENOSUMAB

- Meccanismo alternativo (RANK-L)
- Somministrazione sottocutanea (non DH)
- Minore tossicità ?
- Maggiore efficacia ?

ZOLEDRONATO vs DENOSUMAB: 3 TRIALS


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study

Alison T. Stopeck, Allan Lipton, Jean-Jacques Body, Guenther G. Steger, Kasia Tonkin, Richard H. de Boer, Mikhail Lichinitser, Yasuhiro Fujiwara, Denise A. Yardley, Maria Viniegra, Michelle Fan, Qi Jiang, Roger Dansey, Susie Jun, and Ada Braun

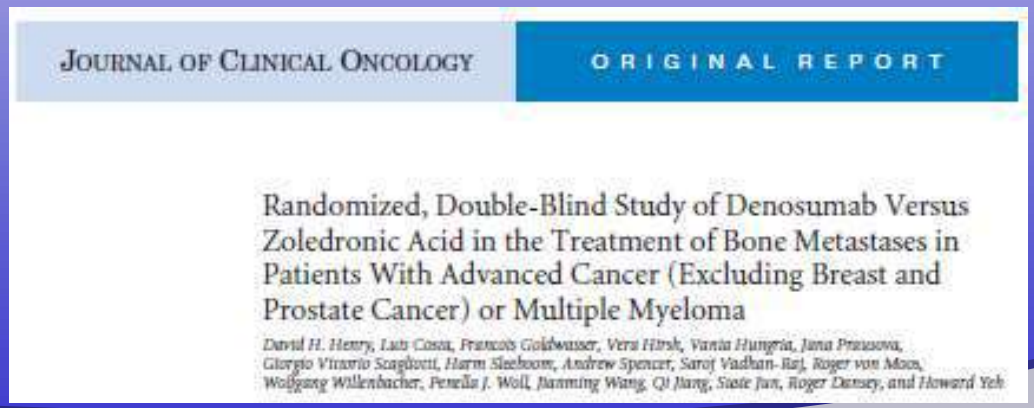
See accompanying editorial doi: 10.1200/JCO.2010.31.0128

Stopeck, JCO 2010
2046 pts
First on-study SRE: HR 0.82
(26.4 months vs not reached)


Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

Karim Fizazi, Michael Carducci, Matthew Smith, Ronaldo Damião, Janet Brown, Lawrence Karsh, Piotr Milecki, Neal Shore, Michael Rader, Huei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl

Fizazi, Lancet 2011
1904 pts
First on-study SRE: HR 0.82 (17.1 vs 20.7 months)


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized, Double-Blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma

David H. Henry, Luis Costa, Francois Goldwasser, Vera Hirsh, Vania Hungria, Jana Prausova, Giorgio Vittorio Scagliotti, Harm Sleeboom, Andrew Spencer, Saroj Vadhan-Raj, Roger von Moos, Wolfgang Willenbacher, Penella J. Woll, Jianming Wang, Qi Jiang, Susie Jun, Roger Dansey, and Howard Yeh

Henry, JCO 2011
1776 pts
First on-study SRE: HR 0.8 (non inferiority) (16.3 vs 20.6 months)

SICMF Società Italiana Chirurgia Maxillo-Facciale

SIPMO Società Italiana di Patologia e Medicina Orale

ONJ NEI TRIALS CON DENOSUMB

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study

Alison T. Stopeck, Allan Lipton, Jean-Jacques Body, Guenther G. Steger, Kasia Tonkin, Richard H. de Boer, Mikhail Lichinitser, Yasuhiro Fujiwara, Denise A. Yardley, Maria Viniegra, Michelle Fan, Qi Jiang, Roger Dansey, Susie Jun, and Ada Braun

See accompanying editorial doi: 10.1200/JCO.2010.31.0128

Stopeck, JCO 2010

ONJ:

2% (DEN) vs 1.4% (ZA)

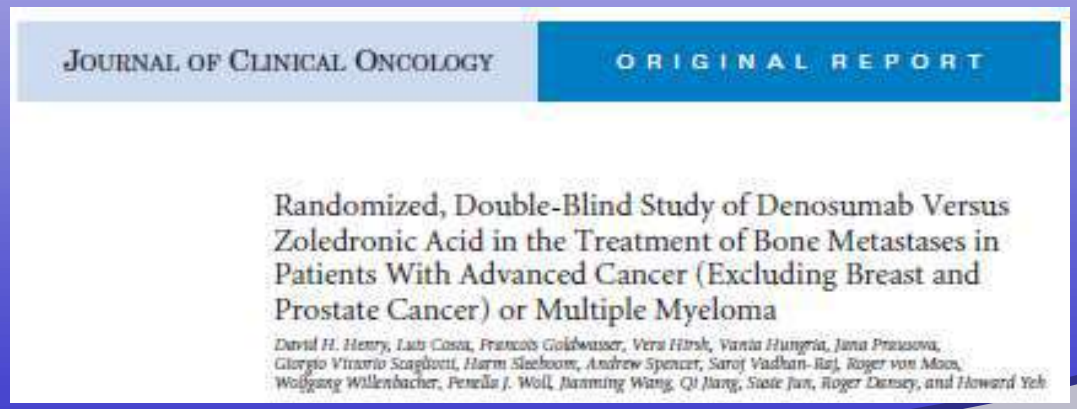
Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

Karim Fizazi, Michael Carducci, Matthew Smith, Ronaldo Damião, Janet Brown, Lawrence Karsh, Piotr Milecki, Neal Shore, Michael Rader, Huei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl

Fizazi, Lancet 2011

ONJ:

2% (DEN) vs 1% (ZA)



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized, Double-Blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma

David H. Henry, Luis Costa, Francois Goldwasser, Vera Hirsh, Vania Hungria, Jana Prausova, Giorgio Vittorio Scagliotti, Harm Sleeboom, Andrew Spencer, Saroj Vadhan-Raj, Roger von Moos, Wolfgang Willenbacher, Pernella J. Woll, Jianming Wang, Qi Jiang, Susie Jun, Roger Dansey, and Howard Yeh

Henry, JCO 2011

ONJ:

1.1% (DEN) vs 1.3% (ZA)

SICMF Società Italiana Chirurgia Maxillo-Facciale

SIPMO Società Italiana di Patologia e Medicina Orale

Frequenza di ONJ dopo zoledronato o denosumab

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Osteonecrosis of the Jaw After Zoledronic Acid and Denosumab Treatment

Vittorio Fusco
Azienda Ospedaliera Santi Antonio e Biagio, Alessandria, Italy

Claudia Galassi
Centro di Prevenzione Oncologica, Azienda Ospedaliera San Giovanni Battista, Torino, Italy

Alfredo Berruti
Azienda Ospedaliera Universitaria San Luigi, Orbassano; Università di Torino, Torino, Italy

Libero Ciuffreda
Centro Oncologico Ematologico Piemontese, Azienda Ospedaliera San Giovanni Battista, Torino, Italy

Cinzia Ortega
Istituto per la Ricerca Contro il Cancro, Candiolo, Italy

Giovannino Ciccone
Centro di Prevenzione Oncologica, Azienda Ospedaliera San Giovanni Battista, Torino, Italy

POSSIBILI CAUSE DI SOTTOSTIMA DELLA FREQUENZA DI ONJ

- ✓ **"Case Adjudication" (AAOMS)**
- ✓ **Selezione dei pazienti**
- ✓ **Breve follow-up**
- ✓ **Incidenza non cumulativa**

Fusco V et al (letter) – J Clin Oncol 2011

Frequenza di ONJ dopo zoledronato o denosumab

Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases

Results: Of 5723 patients enrolled, 89 (1.6%) patients were determined to have ONJ: 37 (1.3%) received zoledronic acid and 52 (1.8%) received denosumab ($P = 0.13$). Tooth extraction was reported for 61.8% of patients with ONJ. ONJ treatment was conservative in >95% of patients. As of October 2010, ONJ resolved in 36.0% of patients (29.7% for zoledronic acid and 40.4% for denosumab).

5723 pts

Event as ***potential*** **ONJ** ***276 (4.8%)***

Adjudicated ONJ cases ***89 (1.5%)***

(according to AAOMS definition)

Saad et al – Ann Oncol 2012

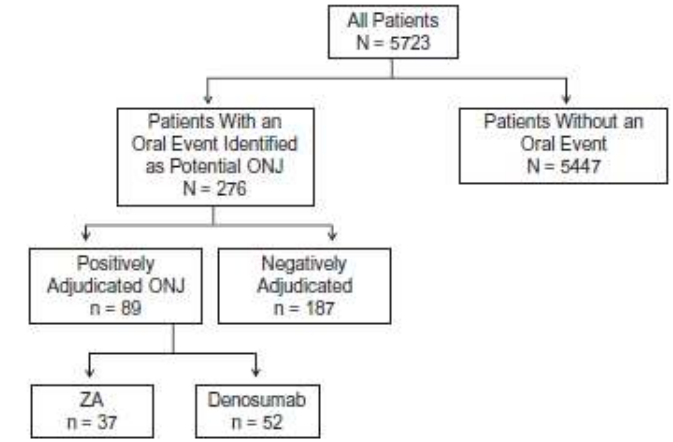


Figure 1. CONSORT diagram. Outcome of ONJ adjudication process. CONSORT, Consolidated Standards of Reporting Trials; ONJ, osteonecrosis of the jaw.

SICMF Società Italiana Chirurgia Maxillo-Facciale

SIPMO Società Italiana di Patologia e Medicina Orale

Denosumab

è . . .

PROLIA, f sc 60 mg ogni 6 mesi
Per OSTEOPOROSI

E

XGEVA, f sc 120 mg ogni mese
Per metastasi ossee, mieloma, TGC

DEFINIZIONE (E STAGING) DI ONJ

American Association of Oral and Maxillofacial Surgeons (AAOMS) medication-related ONJ (MRONJ) staging

Stadio ONJ	caratteristiche
A rischio	Nessun apparente osso necrotico in pazienti trattati con terapie che agiscono sul riassorbimeto osseo
Stadio 0	Non evidenza clinica di osso necrotico, ma aspecifici risultati, cambiamenti radiologici e sintomi
Stadio 1	Osso necrotico esposto, o presenza di fistola collegata all'osso , in pazienti asintomatici senza evidenza di infezione
Stadio 2	Osso necrotico esposto o presenza di fistola collegata all'osso associata ad infezione come evidenziato da dolore ed eritema nella regione esposta dell'osso ± drenaggio purulento
Stadio 3	Osso necrotico esposto o presenza di fistola collegata all'osso in pazienti con dolore, infezione ed 1 o piu' complicazioni*

*osso esposto e necrotico che si estende oltre la regionedell'osso alveolare risultante in frattura patologica, fistola extra orale, comunicazione oroantrale/oronasale o osteolisi che si estende al bordo inferiore della mandibola o al pavimento dei seni nasali

Ruggiero SL, et al. J Oral Maxillofac Surg 2014;72:1938−56.

Tabella 2. Stadiazione clinico-radiologica della ONJ (da "Raccomandazioni clinico-terapeutiche su osteonecrosi delle ossa mascellari associata a bisfosfonati e sua prevenzione". Bedogni A, Campisi G, Fusco V, Agrillo A. Ed. CLEUP, Marzo 2013).

Stadiazione clinico-radiologica BRONJ

Stadio 1

BRONJ FOCALE: in presenza di almeno 1 segno clinico minore e con un *addensamento osseo alla TC limitato al solo processo dento-alveolare** della mandibola o del mascellare, con o senza altri segni radiologici precoci.

Segni clinici minori e sintomi: alitosi, ascesso odontogeno, asimmetria mandibolare, dolore di origine dentale e osseo, esposizione ossea, fistola mucosa, mancata riparazione mucosa alveolare post-estrattiva, mobilità dentale a rapida insorgenza, parestesia/disestesia delle labbra, secrezione purulenta, sequestro spontaneo di frammenti ossei, trisma, tumefazione dei tessuti molli.

Segni TC: *ispessimento trabecolare, osteosclerosi midollare focale*, con o senza ispessimento cresta alveolare e lamina dura, persistenza alveolo post-estrattivo, slargamento spazio parodontale.

a. **asintomatica;**
b. **sintomatica** (presenza di dolore e/o suppurazione).

Stadio 2

BRONJ DIFFUSA: in presenza di almeno 1 segno clinico minore e con un *addensamento osseo alla TC esteso anche al processo basale* della mandibola o del mascellare, con o senza segni radiologici tardivi.

Segni clinici minori e sintomi: come per stadio 1.

Segni TC: *osteosclerosi diffusa*, con o senza fistola oro-antrale e oro-nasale, ispessimento del canale alveolare, reazione periostale, sequestro, sinusite.

a. **asintomatica;**
b. **sintomatica** (presenza di dolore e/o suppurazione).

Stadio 3

BRONJ COMPLICATA: come in stadio 2, in presenza di uno o più dei seguenti:

Segni clinici minori: fistola extra-orale, fuoriuscita di liquidi dal naso, mobilità preternaturale della mandibola con o senza occlusione conservata;

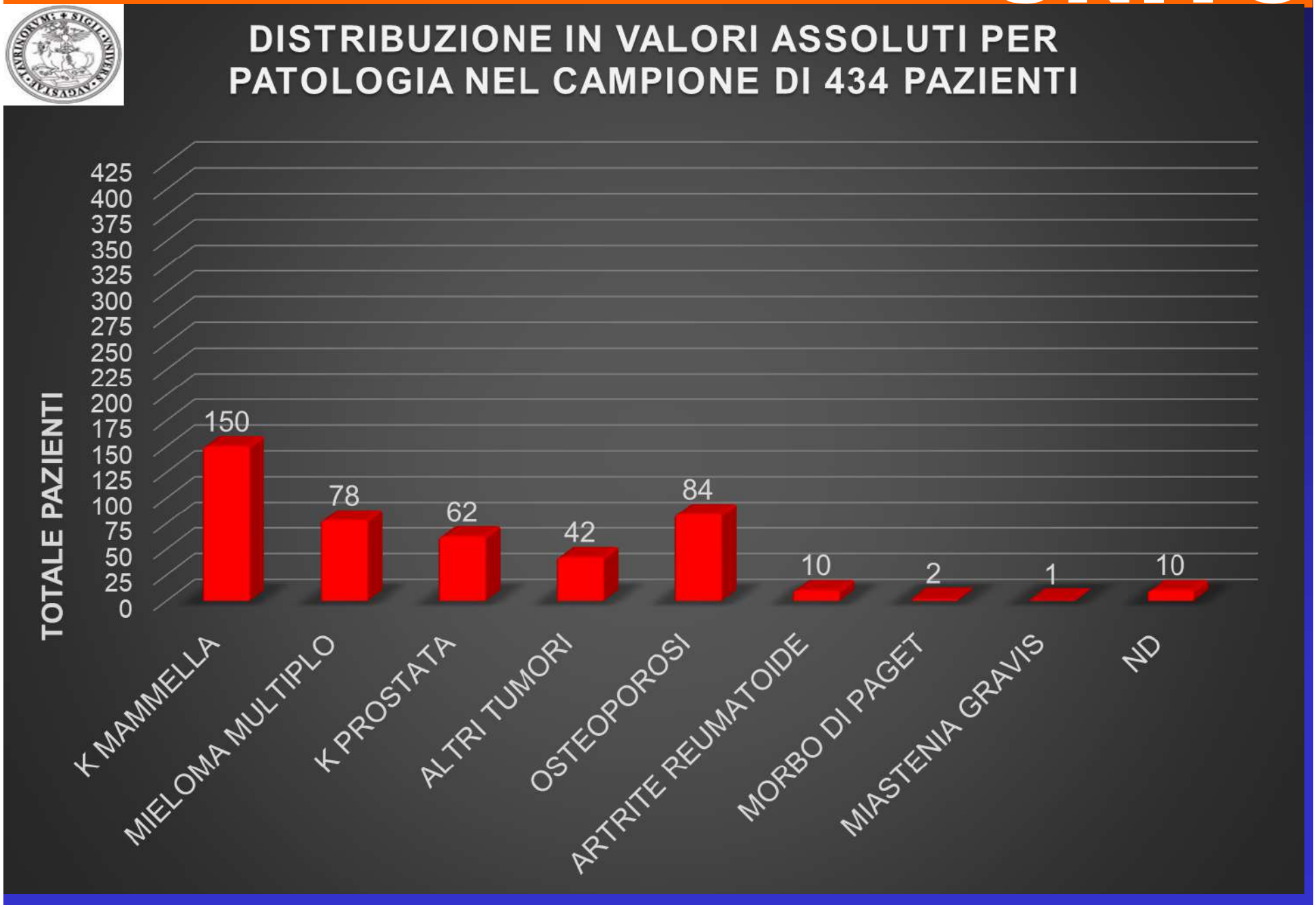
Segni TC: fistola muco-cutanea, frattura patologica, osteolisi estesa al seno mascellare, osteosclerosi di zigomo e/o palato duro.

NB. si intende per regione dento-alveolare quella struttura ossea anatomica che costituisce il supporto scheletrico agli elementi dentari. Per definizione, il processo dento-alveolare termina in senso cranio-caudale subito al di sotto della radice degli elementi dentari

ONJ in Piemonte-VdA 2009-2016

434 nuovi casi !!

UNITO


DISTRIBUZIONE IN VALORI ASSOLUTI PER PATOLOGIA NEL CAMPIONE DI 434 PAZIENTI
TOTALE PAZIENTI
425
400
375
350
325
300
275
250
225
200
175
150
125
100
75
50
25
0
150
78
62
42
84
10
2
1
10
K MAMMELLA
MIELOMA MULTIPLO
K PROSTATA
ALTRI TUMORI
OSTEOPOROSI
ARTRITE REUMATOIDE
MORBO DI PAGET
MIASTENIA GRAVIS
ND

ONJ : Life-threatening or lethal cases

Setabutr 2010, Mondello 2014,
Randi 2014, Yang 2015,

anche in paz osteoporotici

Mehanna 2010, Ebker 2013, Kaehling 2014,

Fulminant course of osteonecrosis of the jaw in a rheumatoid arthritis patient following oral bisphosphonate intake and biologic therapy.

Lethal cervical abscess following bisphosphonate related osteonecrosis of the jaw

Raje et al, Lancet Oncol Mar 2018

Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study

were reported in 144 (17%) versus 106 (12%). Incidence of osteonecrosis of the jaw was not significantly different between the denosumab and zoledronic acid groups (35 [4%] *vs* 24 [3%]; p=0·147). The most common serious adverse

"Adjudicated" ONJ: 4% (denosumab) vs 3% (ZA)

Raje et al, Lancet Oncol Mar 2018

group; appendix pp 47–50); the most common treatment-emergent adverse events that led to discontinuation were musculoskeletal and connective tissue disorders (25 [3%] *vs* 25 [3%]), including osteonecrosis of the jaw (21 [3%] *vs* 14 [2%]), and

35 (4%) patients receiving denosumab and 24 (3%) patients receiving zoledronic acid had positively adjudicated osteonecrosis of the jaw (p=0·147), with most events being grades 1–2 (table 2). Median time to onset of osteonecrosis of the jaw was 17·3 months (IQR 7·8–20·9) for denosumab and 13·6 months (8·1–20·3) for zoledronic acid. Osteonecrosis of the jaw resolved for 12 (35%) patients in the denosumab group and six (25%) patients in the zoledronic acid group, and was ongoing in ten (29%) and eight (33%). Most patients with osteonecrosis of the jaw had known risk factors, such as invasive dental procedures (19 [54%] of 35 patients in the

The risk of osteonecrosis of the jaw is well known for both denosumab and zoledronic acid, and there was no significant difference in incidence between the two groups. The incidence of osteonecrosis of the jaw for both treatment groups was higher in this study than that seen in earlier solid tumour skeletal-related event studies, but was consistent with myeloma studies such as the Myeloma IX trial,[13] indicating that the higher incidence might be related to a longer exposure to the therapies in our trial. Patients with myeloma might be prone to osteonecrosis of the jaw,[2,11,12] in which bone-building osteoblast function is negatively affected and further exacerbated with standard use of corticosteroids. Of particular importance, most adjudicated osteonecrosis of the jaw events were of low grades for both the denosumab and zoledronic acid treatment groups, and the higher resolution frequency for osteonecrosis of the jaw observed in the denosumab group versus the zoledronic acid group might be related to the mechanism inherent to the reversibility of denosumab, unlike bisphosphonates

ONJ rate higher than in other solid tumor trials but consistent with Myeloma IX trial

Most of "low grades"

Raje et al,
Lancet Oncol Mar 2018

Fusco et al, Dentistry Journal 2019 -1

dentistry journal

MDPI

Comment

Osteonecrosis of the Jaw in Myeloma Patients Receiving Denosumab or Zoledronic Acid. Comment on Pivotal Trial by Raje et al. Published on Lancet Oncology

Vittorio Fusco [1,*], Giuseppina Campisi [2], Paul de Boissieu [3], Federico Monaco [4], Anna Baraldi [4], Gianmauro Numico [1] and Alberto Bedogni [5]

Abstract: The recent randomized trial, published by Raje et al., on Lancet Oncology is potentially practice changing. It proposes that denosumab is a valid alternative to zoledronic acid in the treatment of myeloma patients. However, several points need further data and more details, such as information on incidence, diagnosis, and follow-up of osteonecrosis of the jaw (ONJ) cases, observed among treated patients. Adopted definition to adjudicate ONJ cases, type of registration of potential ONJ cases, length of observation are possible causes of potential underestimation of ONJ incidence in their study. Future updated evaluations with longer follow-up, and including actuarial estimation, are required for final judgment on ONJ risk in myeloma patients receiving denosumab, and comparison with ONJ risk by zoledronic acid.

Fusco et al, Dentistry Journal 2019 - 2

Myeloma trial exposure similar to breast trial exposure (lower in other 2 trials)

These reported incidences of "adjudicated" ONJ of 4% and 3%, respectively, are higher values than those previously described in three similar pivotal trials involving bone metastatic cancer patients [2–5], mostly ranging about 1–2%. Raje et al. suggest in the discussion section of their paper that this difference might be related to a longer drug exposure in their study cohorts [1]. However, we analyzed the data from previous trials on monthly administration of zoledronic acid and denosumab in solid cancers [2–6], and we found similar drug exposure and ONJ time to onset (TTO) for the breast cancer cohort, and a little lower exposure in the other two twin trials. We collected for readers' convenience the drug exposure data in a table (see Table 1), showing not large differences.

Fusco et al, Dentistry Journal 2019 - 3

In spite of "preventive" recommendations, invasive dental procedures was reported in 19 out of 35 (denosumab) and 13 out of 24 (ZA) ONJ cases .

The study protocol recommended (see the Methods section in Raje et al.'s study [1]) that oral examinations were performed at enrollment (non-healed dental or oral surgery was a key exclusion criteria) and every six months thereafter. Furthermore, antiresorptive medication discontinuation was recommended (mandatory after August 2015 amendment) [1], 30 days before an elective invasive oral or dental procedure and until complete mucosal healing occurred. In spite of this careful pre-therapy patient selection and management strategy, invasive dental procedures were reported as the main risk factor in 19 out 35 (denosumab group) and in 13 out of 24 (zoledronic acid group) adjudicated ONJ. It would be interesting to know how many patients received dental procedures overall (i.e., the global treated population), and their reasons. To know the reasons of tooth extractions could be of great value. For example, removal of an unexplainably mobile tooth might be not the risk factor for ONJ, but the trigger of bone exposure of an underlying ONJ disease, undetectable without adequate imaging tools (such as computed tomography).

Fusco et al, Dentistry Journal 2019 - 4

ONJ definition changed on 2014 (during the trial)

No clear impact of this change

The myeloma patients were recruited between May 2012 and March 2016, and 59 ONJ cases were "adjudicated" after a median of 17.3 and 13.6 months in the two arms. The definition of ONJ is controversial [7]. The one adopted by Authors seemingly refers to that proposed on 2009 by the Task Force of The American Association of Oral Maxillofacial Surgeons (AAOMS), based on the clinical observation of bone exposure lasting at least eight weeks [8]. Indeed, this definition was revised in 2014 by the same authors, as included cases without bone exposure but only if bone can be probed through a fistula [9]. Non-exposed ONJ (including these latter cases but not limited to them) account for up to 24% of ONJ patients in the literature [7,10,11] and were likely to be overlooked in the present trial. It would be worth to know the influence of this revised definition on the ONJ adjudication process throughout the study, if any.

Fusco et al, Dentistry Journal 2019 - 5

We ask for the number of "potential" ONJ cases

(in solid tumor 89 adjudicated out of 276 potential)

It would be also relevant to know the number of "potential" ONJ cases registered by investigators, and defined by the presence of clinical sign and symptoms suggestive of ONJ, in the two arms. The rate of "potential" ONJ cases could consequently compared with that one registered in previous solid tumors trials, where only 1/3 of the potential ONJ cases were adjudicated (i.e., in solid tumors trials only 89 adjudicated out of 276 potential cases, according to Saad et al.) [6].

Fusco et al, Dentistry Journal 2019 - 6

We ask for long-term evaluation and actuarial risk assessment (Kaplan-Meier)

Lastly, as ONJ risk increases up to 15.5% with longer treatment schedules and observation intervals [12,13] after zoledronic acid, denosumab or their sequence, long-term ONJ estimates of the myeloma study (including actuarial risk assessment) is awaited with great interest.

Raje , reply to Fusco

dentistry journal

MDPI

Comment

Response to Comment—Osteonecrosis of the Jaw in Myeloma Patients Receiving Denosumab or Zoledronic Acid. Comment on Pivotal Trial by Raje et al. Published in Lancet Oncology

Noopur Raje [1,*], Evangelos Terpos [2] and Danielle D. Jandial [3]

1 Center for Multiple Myeloma, Massachusetts General Hospital Cancer Center, Boston, MA 02114, USA
2 School of Medicine, National and Kapodistrian University of Athens, Alexandra General Hospital, 11528 Athens, Greece; eterpos@hotmail.com
3 Amgen Inc., Thousand Oaks, CA 91320, USA; djandial@amgen.com
* Correspondence: NRAJE@mgh.harvard.edu

Received: 31 January 2019; Accepted: 14 April 2019; Published: 16 May 2019

check for updates

Raje , reply to Fusco - 1

We ask for the number of "potential" ONJ cases

(in solid tumor 89 adjudicated out of 276 "potential")

1.5% out of 4.8%

In myeloma :

59 Adjudicated out of 158 potential

3.4 % out of 9.1%

Raje , reply to Fusco - 2

We ask for actuarial estimation

Reply : Exposure-adjusted ONJ incidence rates

2.0 per 100 patient-years in the first year

5.0 per 100 patient-years in the second year

4.5 per 100 patient-years per year thereafter

NO ACTUARIAL CURVES !

Raje , reply to Fusco - 3

Nonethless, invasive dental procedures were reported as a main risk factor in more than half of patients (54%), suggesting that emergent dental procedues continue to occur while on therapy

APPUNTO !!!!

E' COLPA DEI FARMACI !!!

Raje , reply to Fusco - 4

There is no planned follow-up analysis ….

At the end of of the double-blind extension period, patients were offered to continue denosumab therapy for up to an additional two years in an open-label extension (OLE) study …

GIA' FATTO IN BREAST CANCER (Stopeck 2016)

ONJ SALITA A 5.8-8.5% nei vari sottogruppi

MA … HANNO RIFIUTATO DI PRODURRE CURVE ATTUARIALI

Incidence of osteonecrosis of the jaw in patients with bone metastases treated sequentially with bisphosphonates and denosumab

Tine Loyson , Thomas Van Cann, Patrick Schöffski, Paul M. Clement, Oliver Bechter, Isabel Spriet, Ruxandra Coropciuc , Constantinus Politis , Raf O. Vandeweyer, Joseph Schoenaers, Herlinde Dumez, Patrick Berteloot, Patrick Neven, Kristiaan Nackaerts, Feng J. S. H. Woei-A-Jin, Kevin Punie, Hans Wildiers & Benoit Beuselinck

Results: We identified 110 patients sequentially treated with bisphosphonates and denosumab with a median total BRI exposure of 36 months (sequential group). Median bisphosphonates exposure was 16 months and median denosumab exposure was 13 months. About 299 patients were included in the bisphosphonates control group with a median bisphosphonate exposure 19 months. About 6.7% (20/299) of patients developed ONJ. About 240 patients were included in the denosumab control group with a median denosumab exposure 17.5 months. About 10.0% of patients (24/240) developed ONJ. In the sequential group, 15.5% of patients (17/110) developed ONJ. The incidence of ONJ was 1.8% (2/110), 6.3% (6/99), 4.9% (4/82), 5.6% (3/54), and 3.4% (1/29), respectively in the first, second, third, fourth, and fifth year of BRI exposure, an ONJ-incidence similar to ONJ-incidence in the denosumab control group. In a time-to-ONJ-analysis,

110 BP → DENOS; 299 BP only; 240 DENOS only

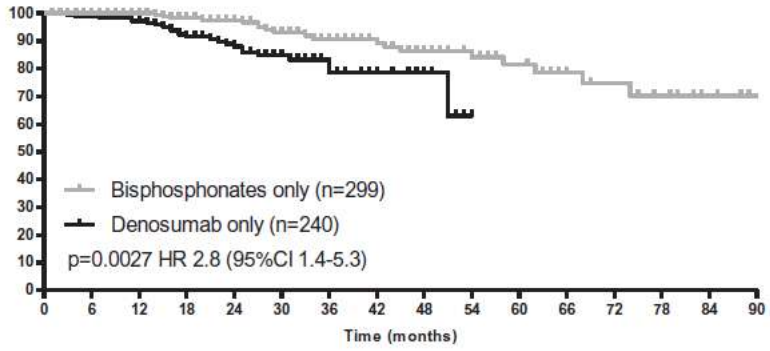
ONJ INCIDENCE : 10 – 15.5% Curve attuariali !

Incidence of osteonecrosis of the jaw in patients with bone metastases treated sequentially with bisphosphonates and denosumab

Tine Loyson , Thomas Van Cann, Patrick Schöffski, Paul M. Clement, Oliver Bechter, Isabel Spriet, Ruxandra Coropciuc , Constantinus Politis , Raf O. Vandeweyer, Joseph Schoenaers, Herlinde Dumez, Patrick Berteloot, Patrick ie, Hans

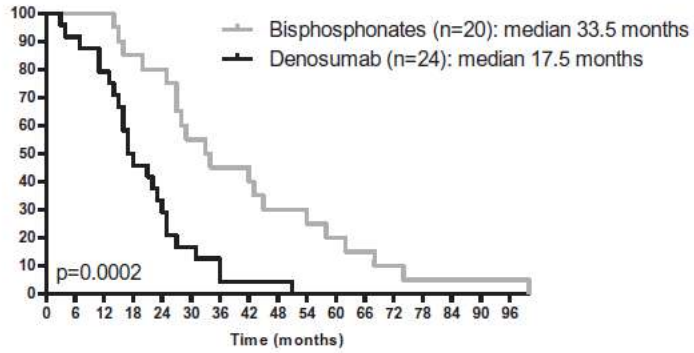
Curve attuariali !

(B) Time-to-ONJ (%):



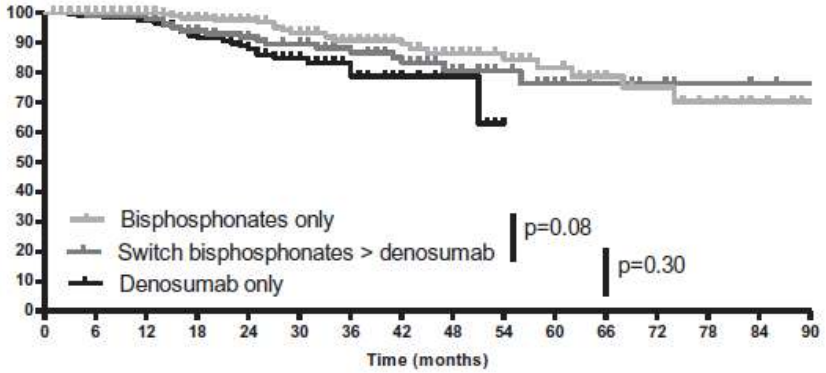
Months	0	12	24	36	48	60	72	84
Bisphosphonates	299	185	126	75	51	31	16	8
Denosumab	240	153	94	36	7	0	0	0

(C) Time-to-ONJ (%) in patients who developed ONJ:



Months	0	6	12	18	24	30	36	42
Bisphosphonates	20	20	20	17	16	11	9	6
Denosumab	24	22	19	12	8	4	3	1

(B) Time-to-ONJ (%):



Months	0	12	24	36	48	60	72	84
Bisphosphonates	299	185	126	75	51	31	16	8
Switch	110	103	83	56	30	16	8	5
Denosumab	240	153	94	36	7	0	0	0

Loyson et al, Acta Clin Belgica 2017

L'esperienza di Asti

Abst **A12 - Denosumab related osteonecrosis of jaw: a single center five-year experience**

F. Testore* 1, M. Canicatti'1, M. Daneo2, M. Austa2, V. Fusco3

1Oncology Unit, Ospedale di Asti, Asti, Italy; 2Maxillofacial Surgery Unit, Ospedale di Asti, Asti, Italy; 3Centro Documentazione Osteonecrosi, Alessandria, Italy

……..

RESULTS: We identified **211 patients receiving denosumab (120 mg every 28 days).** The number of administered courses ranged between 1 and 58. Median number of months of treatment was 11 (range 1-55). Most of patients suffered for breast and prostate tumours; less frequent: melanoma; lung cancer; pancreas and biliary tract cancer; gynecological and urological cancers. At this moment, **ONJ has been identified in 22 patients** (17 treated with denosumab alone and 5 previously receiving zoledronic acid). Characteristics of 22 ONJ cases were analyzed. Sex: 14 female and 8 male. Year of start of denosumab treatment: 2013 in 8, 2014 in 7, 2015 in 4, 2016 in 3 cases. Year of ONJ diagnosis: 2014 in 3, 2015 in 6, 2016 in 8, 2017 in 5. Number of denosumab courses at the ONJ onset time: median 16 (range 3-45); 1-6 in 3 cases; 7-12 in 6 cases; 13-24 in 6 cases; 25-36 in 3 cases; more than 36 in 4 cases. Cancer type was breast in 12, prostate in 6, lung in 3, biliary tract in 1. Other drugs possibly inducing ONJ administered together with denosumab: bevacizumab in 2, everolimus in 2 patients.

CONCLUSIONS: Preliminary results of our centre analysis do not confirm the rate of 1 % - 2 % of "adjudicated" ONJ, according to AAOMS (American Association Oral Maxillofacial Surgeons) definition, in the three denosumab pivotal trials.

ONJ UPDATE 2019

ONJ e MIELOMA
Altri "issues"

-Coesistenza di ONJ e lesioni ossee da MM (varie segnalazioni)

- Pattern genetici (es. Becnel, Leuk Lymphoma 2017)

-Altered microRNA expression profile in lymphoid compartment (Musolino, Ann Hematol 2018)

-Antibioticoterapia (Zadik , Oral Oncol 2018)

MA NON VOGLIO ANNOIARVI OLTRE…

GRAZIE per l'attenzione !