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Osteonecrosi mascellare e mandibolare: epidemiologia

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ONJ nei pazienti oncologici

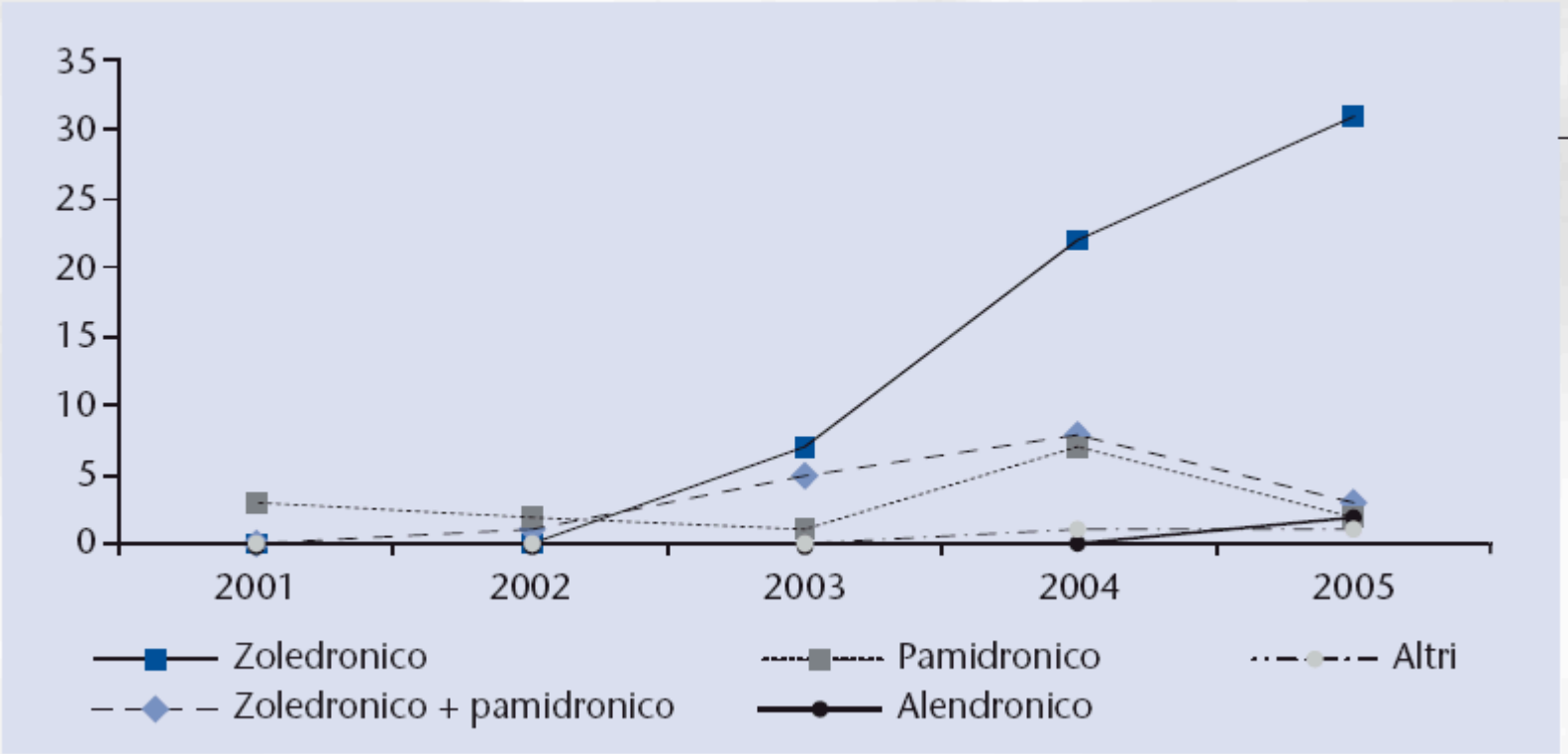
- Pochi reports prima del 2003 (maggior parte : osteoradionecrosi)
- Dicembre 2002 : primo caso di ONJ segnalato alla Novartis
- Da allora, incremento progressivo delle segnalazioni

bollettino d'informazione sui farmaci

Bif XIII N. 2 2006 AIFA - Ministero della Salute

Figura 1 – Andamento temporale delle segnalazioni di osteonecrosi da bifosfonati.

2001- 2/2006



Serie di casi

Utili per:

- Evidenziare il problema
- Suggerire ipotesi su fattori di rischio
- **Studiare il decorso (in maniera prospettica) e i fattori associati alla prognosi**

NON utili per

- stimare incidenza o prevalenza (se non è noto il denominatore
- accertare i fattori di rischio

Frequenza di ONJ

Il reale tasso di incidenza di ONJ associata all'uso di DP è al momento sconosciuto.

Sono disponibili stime di frequenza, basate principalmente su studi retrospettivi tra loro eterogenei per disegno, definizione di caso…

Stime di frequenza di ONJ in pazienti oncologici trattati con DP. Articoli/lettere pubblicati:

	Total cases (%)	Myeloma Pts (%)	Breast C. Pts (%)	Prostate C. Pts (%)
Durie '05		62/904 **(6.8%)**	13/299 **(4.3%)**	
Bamias '05	17/252 **(6.7%)**	11/111 **(9.9%)**	2/70 **(2.9%)**	3/46 **(6.5%)**
Guarnieri '05			3/48 **(6.2%)**	
Dimopoulos'06		15/202 **(7.4%)**		
Badros '06		11/340 **(3.2%)**		
Zervas '06		28/254 **(11.0%)**		
Sanna '06			5/81 **(6.2%)**	
Ortega '06	5/178 **(2.8%)**		2/126 **(1.6%)**	
Tosi '06		9/259 **(3.5%)**		
Pozzi '07		28/1402 **(1.9%)**		
Ortega '07				6/52 **(12%)**
Hoff '08		13/548 **(2.4%)**	16/1338 **(1.2%)**	

Alcuni abstract recenti

	Total cases (%)	Myeloma (%)	Breast (%)	Prostate (%)
Cafro ASH '05	14/118 **(11.9%)**	13/104 **(12.5%)**		
Calvos-Villas EHA '06		7/64 **(10.9%)**		
Wandroo EHA'06		6/26 **(23.1%)**		
Lalayanni EHA '06		6/106 **(6%)**		
Liberati EHA '06		5/64 **(7.8%)**		
Aiti ASCO '06			6/161 **(3.7%)**	
Wallace ASCO '06	3/121 **(2.4%)**		3/76 **(3.9%)**	
Beck ASCO 07			10/310 **(3%)***	
O'Connor ASCO 07	24/354 **(7%)**			
Spadaro ASCO 07			5/100 **(5%)**	
La Verde ASCO 07	15/154 **(9.7%)**			
Katznelson ASCO 07				1/22 **(4.5%)**

* Ca mammella o ginecologici

Stime di frequenza di ONJ in pazienti oncologici trattati con DF
Principali limiti nella confrontabilità delle stime pubblicate:

Diverse modalità di selezione e periodi di reclutamento dei pazienti esposti a DF

Diverse definizioni di caso e di modalità di individuazione di ONJ

Diverse tipi/dosi/durate di trattamento con DF

Diverse durate di follow-up

Difficoltà ad individuare la frequenza in coorti ad alta mortalità

Fattori di rischio

- **Dose cumulativa**

Hoff et al, JBMR 2008:

it is evident that development of ONJ was associated with

- longer median duration of malignant disease,
- longer median duration of bone metastases

which relates to

- **longer treatment duration**,
- and **greater cumulative doses of IV DF**

Hoff et al, JBMR 2008

esposizione tra 9/1996 - 2/2004, follow-up al 6/2005

		Anni di trattamento (range)	Dose mediana mg (range)
Breast cancer patients (16/1338)			
		PAMIDRONATO IV	
	ONJ	**1.7 (0.9-4.2)**	**1710 (90-3510)**
	Non ONJ	**0.6 (0.0-8.4)**	**540 (45-9810)**
		ZOLEDRONATO IV	
	ONJ	**2.0 (0.2-5.9)**	**68 (8-132)**
	Non ONJ	**0.7 (0.0-4.1)**	**32 (4-270)**

Wilkinson GS et al, J Natl Cancer Inst 2007;99: 1016 – 24

Table 3. Hazard ratios for adverse outcomes associated with cumulative dose and patient characteristics among 16073 patients who received intravenous bisphosphonates*

Cumulative dose or characteristic	Inflammatory conditions or osteomyelitis of the jaw, HR (95% CI)	Operation on jaw and facial bones, HR (95% CI)
Equivalent dose†		
≤3	1.00 (referent)	1.00 (referent)
4–8	1.56 (0.67 to 3.60)	3.63 (0.77 to 17.08)
9–13	1.82 (0.75 to 4.39)	5.91 (1.24 to 28.19)
14–21	3.02 (1.28 to 7.10)	8.72 (1.82 to 41.89)
>21	3.57 (1.46 to 8.75)	9.18 (1.74 to 48.53)

* Matched bisphosphonate users (n = 14349) and nonusers (n = 28698). HR = hazard ratio; CI = confidence interval.

† Cox proportional hazard model was adjusted for age; ethnicity; sex; type of cancer; bone metastasis; Surveillance, Epidemiology, and End Results region; year of drug administration; comorbidity; risk index; and use of intravenous steroids.

* HR = hazard ratio; CI = confidence interval.

† Equivalent doses (considered as one dose) were 90 mg for pamidronate and 4 mg for zoledronic acid.

Fattori di rischio

- **Tipo di difosfonato usato (potenza) e via di somministrazione**

IV DF >>> Oral DF

IV Zoledronato > IV Pamidronato

28 casi di ONJ / 254 pazienti con mieloma

Table II. Independent prognostic variables for the development of osteonecrosis of the jaw according to a multivariate Cox analysis.

Parameter	Relative risk (95% confidence interval)	*P*-value
Pamidronate alone, 0 cycles of administration and no thalidomide	1·00	
Zoledronic acid alone	9·5 (1·0–83·2)	0·042
Subsequent use of pamidronate and zoledronic acid	2·1 (0·2–18·0)	0·495
Cycles of bisphosphonate administration	4·9 (1·9–9·9)	0·012
Thalidomide use	2·4 (1·0–5·7)	0·043

Zervas K et al, British Journal Haematology 2006

Fattori di rischio

- Storia di procedure dentistiche e /o flogosi acute e croniche ripetute

Nello studio di Durie (2005, web survey), una storia di problemi dentali era riportata nell'81% dei pazienti con mieloma e nel 69% dei pazienti con breast cancer che avevano ONJ.

Nei pazienti senza ONJ era del 33%.

Storia di procedure dentistiche e /o flogosi acute e croniche ripetute: quale ruolo?

Altundag K, 2006
TOOTH EXTRACTION: IS IT INCITING EVENT OR SEQUELA OF OSTEONECROSIS OF THE JAWS ASSOCIATED WITH INTRAVENOUS BISPHOSPHONATES?

Estrazione dentale → ONJ ?

ONJ “latente” → Estrazione dentale ?

In ogni caso ….

PREVENTION OF BRONJ

Prior to treatment with an *IV bisphosphonate*, the patient should have a thorough oral examination, any unsalvageable teeth should be removed, all invasive dental procedures should be completed, and optimal periodontal health should be achieved.

American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws.
J Oral Maxillofac Surg 65:369-376, 2007

Quali altri fattori di rischio?

?

Altri fattori ipotizzati

- *Chemioterapia?*
- *Cortisonici?*
- *Fumo?*
- *Diabete?*
- *Obesità?*
- *….*
- *….*

J Oral Maxillofac Surg 66:625-631, 2008

Zoledronate, Smoking, and Obesity Are Strong Risk Factors for Osteonecrosis of the Jaw: A Case-Control Study

John H. Wessel, BS, Thomas B. Dodson, DMD, MPH,† and Athanasios I. Zavras, DMD, DrMS‡*

Studio caso-controllo piemontese

- Casi di ONJ rilevati attivamente
- Controlli appaiati per data di diagnosi di MTS, tipo di tumore, sesso, ospedale, sopravvivenza
- Informazioni su terapia con DF, terapie concomitanti, eventuali fattori di rischio da cartelle cliniche
- Obbiettivi: studiare l'effetto del tipo di farmaco, via di somministrazione, dose cumulativa, chemioterapia, radioterapia, eventuali fattori di rischio

Conclusioni

- Follow-up delle casistiche di ONJ
- Stime di incidenza. Mantenere una stretta sorveglianza degli eventi nel tempo (definire una codifica univoca?)
- Studiare la relazione dose-risposta (soglia?) e i fattori di rischio

FINE

Hoff et al, JBMR 2007

esposizione tra 9/1996 - 2/2004, follow-up al 6/2005

		Anni di trattamento (range)	Dose mediana mg (range)
Multiple myeloma patients (13/548)			
		PAMIDRONATO IV	
	ONJ	**1.6 (0.0-3.1)**	**1800 (90-2520)**
	Non ONJ	**0.3 (0.0-6.7)**	**270 (30-9300)**
		ZOLEDRONATO IV	
	ONJ	**1.9 (0.7-2.9)**	**58 (28-152)**
	Non ONJ	**0.7 (0.0-3.6)**	**24 (4-172)**

Wilkinson GS et al, J Natl Cancer Inst 2007;99: 1016 – 24

Table 2. Hazard of jaw complications associated with bisphosphonate therapy*

Outcome	Bisphosphonate use	No. of events	Adjusted HR (95% CI)†
Inflammatory conditions or osteomyelitis of the jaw	No	15	1.00 (referent)
	Yes	81	11.48 (6.49 to 20.33)
Operations on facial bones	No	25	1.00 (referent)
	Yes	41	3.15 (1.86 to 5.32)
Either outcome	No	38	1.00 (referent)
	Yes	95	4.94 (3.33 to 7.34)

* Matched bisphosphonate users (n = 14349) and nonusers (n = 28698). HR = hazard ratio; CI = confidence interval.

† Cox proportional hazard model was adjusted for age; ethnicity; sex; type of cancer; bone metastasis; Surveillance, Epidemiology, and End Results region; year of drug administration; comorbidity; risk index; and use of intravenous steroids.

IV DF >>> Oral DF

Mavrokokki et al, 2007

The frequency of ONJ in bone malignancy cases, treated with mainly intravenous zoledronate or pamidronate was 1 in 87 to 114 (0.88% to 1.15%).

The frequency of ONJ in osteoporotic patients, mainly on weekly oral alendronate was 1 in 2,260 to 8,470 (0.01% to 0.04%) patients.

IV Zoledronato > IV pamidronato

Our results and reports from others (7-9, 11) suggest an increase in the recognition of this disorder coincident with the approval of zoledronic acid, the most potent bisphosphonate.

Indeed, the multivariate analysis of our data set shows that the use of zoledronic acid is an independent risk factor in women with breast cancer.

In addition, among breast cancer patients who developed osteonecrosis of the jaw, the time between initiating bisphosphonate therapy to development of osteonecrosis of the jaw was shorter in patients treated with zoledronic acid alone when compared to patients treated with pamidronate or pamidronate followed by zoledronic acid.

Hoff et al, JBMR 2008

ONJ in Patients Treated With **Oral** BPs for Osteoporosis

Table 3 Rate of oral bisphosphonate-related ONJ in the literature (studies which included at least 10 patients)

Study	No. of ONJ patients	Gender		No. of oral bisphosphonate related ONJ (%)	Underlying disease (n)	Medications (n)
		Male	Female			
Marx et al. [3]	119	NS	NS	3 (2.5)	Osteoporosis (3)	Alendronate (3)
Ruggiero et al. [4]	63	18	45	6 (9.5)	Osteoporosis (6)	Alendronate (5) Risedronate (1)
Farrugia et al. [5]	23	7	16	5 (21.7)	Osteoporosis (4) Paget's dis. (1)	Alendronate (5)
Migliorati et al. [6]	18	4	14	1 (5.6)	Osteoporosis (1)	Alendronate (1)
Purcell & Boyd [7]	13	7	6	1 (7.7)	Osteoporosis (1)	Alendronate (1)
Shlomi et al. [8]	11	3	8	3 (27.3)	Osteoporosis (3)	Alendronate (3)
Total	247	-	-	19 (7.7)	Osteoporosis (18) Paget's disease (1)	Alendronate (18) Risedronate (1)

NS - not specified

N. Yarom, et al
Osteonecrosis of the jaw induced by orally administered bisphosphonates: incidence, clinical features, predisposing factors and treatment outcome
Osteoporos Int 18:1363–1370, 2007

American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws.
J Oral Maxillofac Surg 65:369-376, 2007

The specialty's experiences have identified several BRONJ cases related to oral bisphosphonates. 22,24
Patients under treatment with oral bisphosphonate therapy are at a considerably lower risk for BRONJ than patients treated with IV bisphosphonates. Based on data from the manufacturer of alendronate (Merck, Whitehouse Station, NJ), the incidence of BRONJ was calculated to be 0.7/100,000 person/years of exposure.44 This was derived from the number of reported (not confirmed) cases that were deemed to likely represent BRONJ divided by the number of alendronate pills prescribed since approval of the drug, and converted to number of patient years. Although these are the best available data to date, there may be serious under-reporting and, as noted above, none confirmed.

Correspondence with Alastair Goss, DDSc (September 2006) reported that the estimated incidence of BRONJ for patients treated weekly with alendronate is 0.01% to 0.04%, based on prescription data in Australia. After extractions, this rate increased to 0.09% to 0.34%.