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內文：

INDICATIONS AND BENEFITS OF BISPHOSPHONATE THERAPY

IV Bisphosphonates

→cancer-related conditions (hypercalcemia of malignancy, bone metastases in solid tumors such as breast cancer, prostate cancer, lung cancer, and lytic lesions in the setting of multiple myeloma)→improve quality of life for p't with advanced cancer.

◈ Pamidronate(Aredia), Zoledronic acid(Zometa), Zoledronate(Reclast), Ibandronate(Boniva)

Oral Bisphosphonates

➢ most prevalent and common indication→osteoporosis

➢ Paget's disease of bone and osteogenesis imperfecta of childhood.

	Primary Indication	Nitrogen Containing	Dose	Route	Relative Potency*
Etidronate (Didronel)	Paget's disease	No	300-750 mg daily for 6 mo	Oral	1
Tiludronate (Skelid)	Paget's disease	No	400 mg daily for 3 mo	Oral	50
Alendronate (Fosamax)	Osteoporosis	Yes	10 mg/d 70 mg/wk	Oral	1,000
Risedronate (Actonel)	Osteoporosis	Yes	5 mg/d 35 mg/wk	Oral	1,000
Ibandronate (Boniva)	Osteoporosis	Yes	2.5 mg/d 150 mg/mo 3 mg every 3 mo	Oral IV	1,000
Pamidronate (Aredia)	Bone metastases	Yes	90 mg/3 wk	IV	1,000-5,000
Zoledronate (Zometa)	Bone metastases	Yes	4 mg/3 wk	IV	10,000+
Zoledronate (Reclast)	Osteoporosis	Yes	5 mg/yr	IV	10,000+

BRONJ Case Definition

◈ *Patients may be considered to have BRONJ*

1. Current or previous treatment with a bisphosphonate

2. Exposed bone in the maxillofacial region that has persisted for more than 8 weeks

3. No history of radiation therapy to the jaws

Estimated Incidence and Factors Associated With Development of BRONJ

IV BISPHOSPHONATES AND INCIDENCE OF BRONJ

→0.8% to 12%

ORAL BISPHOSPHONATES AND INCIDENCE OF BRONJ

- considerably lower risk of BRONJ than cancer patients treated with monthly IV bisphosphonates.
- the incidence of BRONJ was calculated to be 0.7/100,000 person-years of exposure(Merck)→underreporting.
- Surveillance data from Australia estimated the incidence of BRONJ for patients treated weekly with alendronate as 0.01% to 0.04%
- 13,000 Kaiser-Permanente members, the prevalence of BRONJ in patients receiving long-term oral bps. was reported at 0.06%
- IV>>oral.
- It is important to accurately determine the incidence of BRONJ with long-term use (ie, longer than 3 years) of oral bisphosphonates.

RISK FACTORS

1. Drug-related risk factors
   A. Bisphosphonate potency: zoledronate (Zometa)>pamidronate (Aredia)>oral bps.
   B. Duration of therapy
2. Local risk factors
   A. Dentoalveolar surgery: 5-~21-fold increased risk in IV bisphosphonates treated cancer patients.
   B. Local anatomy: mandible: maxilla=2:1(more commonly in areas with thin mucosa overlying bony prominences such as tori, bony exostoses, and the mylohyoid ridge)
   C. Concomitant oral disease: history of inflammatory dental disease (eg, periodontal and dental abscesses) are at a 7-fold increased risk.
3. Demographic and systemic factors
   A. increasing age ; whites.
   B. systemic factor(renal dialysis, low hemoglobin, obesity, and diabetes)
   C. chemotherapeutic agents (ie, cyclophosphamide, erythropoietin, and steroids)

D. Wessel et al reported an increased risk among tobacco users, but no increased risk was associated with alcohol exposure.

4. Genetic factors

→Sarasquete et al (single nucleotide polymorphisms, in the cytochrome P450-2C gene [CYP2C8])

5. Preventive factors

→The 2 largest risk factors for BRONJ are IV bisphosphonate exposure and dentoalveolar procedures.

Prevention of BRONJ

- Dental evaluations and treatment before initiating IV bisphosphonate therapy among cancer patients reduces the BRONJ risk.
- BRONJ increase when the duration of therapy(oral Bps.) exceed 3 years. The period can be shortened in the presence of corticosteroid.
- If systemic conditions permit, consider discontinuation of oral Bps. for a 3month period bofore and 3-month period after dental treatment

Treatment goal

◈ *Patients About to Initiate IV:*

A. If systemic conditions permit, initiation of bisphosphonate therapy should be delayed until the dental health has been optimized.

B. If systemic conditions permit, until the extraction site has mucosalized (14 to 21days) or until adequate osseous healing has occurred.

C. Patients be educated as to the importance of dental hygiene and regular dental evaluations and specifically instructed to report any pain, swelling,or exposed.

◈ *Asymptomatic Patients Receiving IV Bisphosphonates:*

A. Procedures that involve direct osseous injury should be avoided.

B. The efficacy of a drug holiday for patients receiving yearly zoledronic acid therapy and the appropriate timing of dentoalveolar surgery (if required) is unknown and requires additional study.

◈ *Asymptomatic Patients Receiving Oral Bisphosphonate Therapy:*

A. *It is recommended that patients be adequately informed of the small risk of compromised bone healing.*

B. *The use of bone turnover marker levels, in conjunction with a drug holiday, has been reported as an additional tool to guide treatment decision.* → *need additional research.*

C. *For individuals who have taken an oral bisphosphonate for fewer than 3 years and have no clinical risk factors,→no alteration or delay in the planned* surgery is necessary.

D. For those patients who have taken an oral bisphosphonate for fewer than 3 years and have also taken corticosteroids concomitantly → consider discontinuation of the oral bisphosphonate (drug holiday) for at least 3 months before oral surgery, if systemic conditions permit.

◈ *Patients with BRONJ*

A. treatment objectives →eliminate pain, control infection of the soft and hard tissue, and minimize the progression or occurrence of bone necrosis

B. Surgical debridement is effective in eradicating the necrotic bone(difficult to obtain a surgical margin in early stage.)→ Surgical treatment should be delayed if possible and reserved for those patients with stage 3 disease or in those cases with well-defined sequestrum.

C. Stage 3 disease might require resection and immediate reconstruction with a reconstruction plate or an obturator.

D. Hyperbaric oxygen therapy has some improvement in wound healing and long-term pain scores, but its use as the sole treatment modality for BRONJ cannot be supported at this time.

E. Other non-invasive treatment: platelet-rich plasma, parathyroid hormone, and bone morphogenic protein-->need more study.

Staging and Treatment Strategies

Patient at risk: no apparent necrotic bone in asymptomatic patients who have been treated with IV or oral bisphosphonates.

Stage 0: patient with no clinical evidence of necrotic bone, but who present with nonspecific symptoms or clinical and radiographic findings, include:

◈ Symptoms:

1. Odontalgia not explained by an odontogenic cause
2. Dull, aching bone pain in the body of the mandible
3. Sinus pain(could be associated with inflammation and thickening of the maxillary sinus wall)
4. Altered neurosensory function

◈ Clinical findings:

1. Loosening of teeth not explained
2. fistula not associated with pulpal necrosis due to caries

◈ Radiographic findings:

1. Persistence of unremodeled bone in sockets

2. Thickening/obscuring of periodontal ligament

3. Inferior alveolar canal narrowing

Stage 1: exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection.

Stage 2: exposed and necrotic bone in patients with pain and clinical evidence of infection (pain, erythema, purulent drainage)

Stage3: exposed and necrotic bone in patients with pain, infection, and one or more of the following:
1. Exposed necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla)

2. Pathologic fracture

3. Extraoral fistula

4. Oral antral/oral nasal communication

5. Osteolysis extending to the inferior border of the mandible or sinus floor

Treatment strategies

At risk: Not require any treatment.

Patient education.

Stage 0: Systemic management, including use of pain medication and antibiotics

Stage 1: Antibacterial mouth rinse(0.12% CHX)

Clinical follow-up

No surgical treatment is indicated.

Stage2: Symptomatic treatment with oral antibiotics (Presence of Actinomyces species→antibiotic regimen should be adjusted)

Oral antibacterial mouth rinse

Pain control

Superficial debridement to relieve soft tissue irritation.

Stage3: Antibacterial mouth rinse

Antibiotic therapy and pain control

Surgical debridement/resection for longer term palliation of infection and pain.

◈ *Regardless of disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone*

- ◈ *Extraction of symptomatic teeth within exposed, necrotic bone should be considered because it is unlikely that extraction will exacerbate established necrotic process.*
- ◈ *Discontinuation of IV Bps. has shown no short-term benefit. If systemic conditions permit, long-term discontinuation might be beneficia.*
- ◈ *Discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution after debridement surgery.*
- ◈ *If systemic conditions permit, modification or cessation of oral bisphosphonate therapy should be done in consultation with treating physician and patient*

題號	題目
1	骨壞死(osteonecrosis)常因以下幾點risk factor的存在，而增加其發生率。以下何者非其risk factor? (A) Teeth (B) Bone trauma (C) Periodontal disease (D) Antibody therapy
答案(D)	出處：Oral& Maxillofacial pathology p.263
題號	題目
2	顎骨壞死常見於頭頸部腫瘤放射線治療後的病患。報告指出發生率約為4%，甚有其他研究指出發生率可能達到22%之高。以下關於放射性骨壞死的描述何者有誤？
	(A) 只要覆蓋其上的表皮是完整，疾病早期可能是無症狀的。 (B) 高壓氧治療是有效的，因為它可增進血管生成(angiogenesis) (C) 骨壞死的情形在放射線治療完的一個星期左右即產生症狀。 (D) 核子骨骼造影(radionuclide bone scan)對於是否有ORN的檢查，是有幫助的。
答案(C)	出處：differential diagnosis of oral and maxillofacial lesion Pg.436