Bisphosphonates
- Guidelines status in 2007 -

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Classical guidelines

SOLID TUMORS: Hillner et al., J Clin Oncol 2003
* Bone loss in breast cancer: Hillner et al., J Clin Oncol 2003

MYELOMA: Kyle et al, J Clin Oncol 2000

Updated guidelines / European view

SOLID TUMORS: Aapro et al., Ann Oncol 2007
* Elderly: Body et al., Eur J Cancer 2007
* Al-induced bone loss: Aapro, Body, Brufsky, Coleman, Guise, Hadji, Lipton, Tubiana [manuscript in preparation]

MYELOMA: Kyle et al, J Clin Oncol 2007
BONE METASTASES

Breast cancer

4 BPs are approved

- oral clodronate [ 1600 mg/d ]
- iv pamidronate [ 90 mg over 2h ]
- oral & iv ibandronate [ 50 mg/d; 6mg over 15 min ]
- iv zoledronate (zoledronic acid) [ 4 mg over 15 min ]

* Amino BPs are recommended
zoledronate > pamidronate (multiple-event analysis; lytic lesions subgroup)

* Route of administration: iv « most often preferable »
but consider oral for patients who cannot or do not need to attend regular hospital care
**Prostate cancer**

- Benefit demonstrated only for zoledronate in hormone-refractory patients

  ? Do not wait for symptoms before starting therapy
  (cf. SRE reduction greatest in patients without pain)

**Other solid tumors**

- Benefit demonstrated for zoledronate across a wide range of tumors (NSCLC, kidney)

  ! Take into account expectation of overall palliative benefit & expected survival time
Bisphosphonates for metastatic breast cancer

- ? WHEN TO START? -

(from Hillner et al., ASCO 2003 update, JCO 2003)

* evidence of bone destruction on plain x-rays
* abnormal bone scan and an abnormal CT or MRI scan showing bone destruction: « reasonable »
* only abnormal bone scan: « not recommended »
Bisphosphonates for metastatic breast cancer
- WHEN TO STOP ? -

ASCO guidelines (2003)
« … continued until evidence of substantial decline
in a patient’s general performance status »

BUT 2 years’ trials !

==> stop after 2 years ? : NOT systematically !

==> decrease infusion frequency after 2 years ?
e.g. every 3 months … BUT no data!
Optimal use of bisphosphonates

! Paucity of data !

* Initiation of therapy in breast cancer
  consider the start of therapy as soon as bone metastases are diagnosed by radiographic techniques, even if there are no symptoms

* Continuation of therapy beyond 2 years
  based on an individual risk assessment over the long term
  reduce the frequency of SREs
  reduce bone pain & maintain QoL

? Use of bone markers to direct therapy:
  not currently recommended (under investigation)
Adverse events associated with bisphosphonate therapy

* acute phase reactions
* hypocalcemia (prevented with Ca & vit D supplements)
* NEPHROTOXICITY
  specific monitoring recommended for pamidronate & zoledronate

Creatinine clearance:
- 30-60 ml/min: reduce dose of zoledronate
  - ? increase infusion time of pamidronate
- < 30 ml/min: only a lower dose of ibandronate (2 mg) is recommended

* OSTEONECROSIS OF THE JAW
  etiology is unclear and multifactorial
  ... but is dependent on duration of BP therapy
Specific recommendations in elderly patients

* No specific trials!

* BPs are recommended but safety precautions are particularly important:
  - monitor creatinine clearance
  - assess and optimize hydration therapy
  - elderly patients *may* be at particular risk from ONJ

Subanalyses of phase III trials (zoledronate and ibandronate) do not suggest an increased potential for nephrotoxicity:
Renal function deterioration during the core study by age
(≤ 70, > 70 yrs)
-For post 15-minutes infusion amendment safety evaluable patients-

<table>
<thead>
<tr>
<th></th>
<th>Age ≤ 70 (n/N)</th>
<th>Age &gt; 70 (n/N)</th>
<th>Difference between age groups (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast Cancer and Multiple Myeloma</strong></td>
<td></td>
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<tr>
<td>Zoledronate 4 mg</td>
<td>9.1% (20/219)</td>
<td>7.5% (4/53)</td>
<td>-1.6% (-10.1%, 6.9%)</td>
</tr>
<tr>
<td>Pamidronate 90 mg</td>
<td>8.2% (18/219)</td>
<td>8.2% (4/49)</td>
<td>-0.1% (-8.6%, 8.4%)</td>
</tr>
<tr>
<td>Difference between treatment groups (95% CI)</td>
<td>0.9% (-4.4%, 6.2%)</td>
<td>-0.6% (-11.1%, 9.8%)</td>
<td></td>
</tr>
</tbody>
</table>

| **Prostate Cancer and Other Solid Tumors** |                |                |                                      |
| Zoledronate 4 mg         | 11.0% (19/172) | 15.3% (13/85)  | 4.2% (-4.3%, 12.8%)                 |
| Placebo                  | 6.4% (10/156)  | 11.8% (10/85)  | 5.4% (-1.9%, 12.6%)                 |
| Difference between treatment groups (95% CI) | 4.6% (-1.5%, 10.8%) | 3.5% (-6.8%, 13.8%) | |
- Ibandronate -

Time to renal function deterioration in the elderly

\[ \geq 65 \text{ yrs}: \text{placebo 22 \% (35/158), ibandronate 6 mg 25 \% (39/154)} \]
Appropriate dental care before starting bisphosphonates in ALL patients

* inform the patient on the risk of ONJ

* comprehensive dental examination

* appropriate dentistry by a dental specialist

* maintain good oral hygiene

* dental examinations at 6- to 12- month intervals and avoid invasive dental procedures during BP therapy
Management of patients who have developed bisphosphonate-associated ONJ

* avoid invasive surgery
  prefer minimal necrotic bone debridement
  aggressive treatment of infection

* discontinue bisphosphonate therapy?
  NO data to support or refute!

  in general, BPs should be discontinued until the lesion has healed but the decision is function of the aggressiveness of the bone disease

  versus switch to a non-aminobisphosphonate, i.e. clodronate?
  … if available
  BUT … NO data!
Breast cancer: adjuvant setting

* Prevention of bone metastases
  
  BPs are not recommended
  
  ... pending the results of ongoing trials

* Aromatase inhibitor-induced bone loss
  
  • steroidal (exemestane) and non-steroidal AIs are associated with bone loss and an increased risk of fractures
  
  • bone loss can be prevented with bisphosphonates
    
    strongest evidence for zoledronate
    
    take into account bone mass
    
    and validated risk factors for fractures
ASCO 2007 Guideline Update on the role of the BPs in multiple myeloma

Kyle et al., JCO 2007

* Recommend to start BPs for MM patients who have (plain X-rays or imaging studies) lytic destruction of bone or spine compression fracture from OPsis
  - iv pamidronate 90 mg over ≥ 2 hrs
  - iv zoledronate 4 mg over ≥ 15 min
« clodronate is an alternative BP » where available

* « Reasonable » in patients with « osteopenia » (X-rays or BMD)

* « Not recommended » in patients with solitary plasmacytoma or smoldering or indolent myeloma
* Suggest that BPs are administered monthly for a period of 2 years (≈ 1 yr: cf randomized trial of Corso et al., Leukemia 2007)

* At 2 years: seriously consider stopping BPs in patients with responsive or stable disease

  Resume therapy upon relapse with new-onset SREs

* ! Monitor renal function
  
  ! Comprehensive dental examination and appropriate preventive dentistry before BP therapy
SUMMARY
- EFFICACY OF BISPHOSPHONATES -

1. Reduction of skeletal morbidity rate:
   - **Breast cancer**: hazard ratio to develop an SRE lowered to ~ 0.60 as compared to placebo (zoledronate, ibandronate) but NO direct comparisons;
   - zoledronate > pamidronate (multiple-event analysis)
   - **Myeloma**: zoledronate = pamidronate
   - **Prostate cancer**: only zoledronate

2. Analgesic effect: acute and chronic

3. **Al-induced bone loss**: increasing role of BPs

4. **Lack** of specific studies in the **elderly**
SUMMARY
- SAFETY OF BISPHOSPHONATES -

1. Nephrotoxicity
   easily manageable in most patients
   no evidence that BPs lead to an increased risk of toxicity
   in the elderly BUT…

2. Osteonecrosis of the jaw
   linked to duration of BP therapy
   (consider individualization of BP therapy)
   prevention!

3. Oral BPs
   tolerance appears to be good but
   compliance may be a problem