Update on bisphosphonates and Denosumab

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Update on Bisphosphonates and Denosumab

• How do they work
• Indications
• Which drug and how often?
• Adverse effects
Pathophysiology of bone mets

1. Tumour cells produce factors that stimulate osteoblasts to secrete RANKL.

2. Osteoblasts and other bone cells increase expression of RANKL.

3. Over-expression of RANKL drives increased formation, function and survival of osteoclasts, leading to excessive bone resorption.

4. Bone resorption releases growth factors from the bone matrix that may perpetuate tumour activity.
Bisphosphonates

Nitrogen containing
• Pamidronate
• Alendronate
• Ibandronate
• Risendronate
• Zoledronic acid

Non-nitrogen containing
• Etidronate
• Clodronate
• Tiludronate
Indications

• Prevention and treatment of osteoporosis
• Pagets disease of bone
• Giant cell tumour of bone
• Treatment of hypercalcaemia of malignancy
• Adjuvant anti-cancer agents in breast cancer
• Reduction in skeletal related events (SREs)
• Pain control
Hypercalcaemia of malignancy

• Zoledronic acid superior to Pamidronate
• Denosumab may have a role in bisphosphonate refractory hypercalcaemia or where severe renal impairment precludes bisphosphonates

Anticancer agents

• Small reductions in distant recurrence rate and breast cancer mortality at 10 years from bisphosphonates
• Benefit almost exclusively post-menopausal women
• Zoledronic acid 4mg 6 monthly 3-5 years or Oral Clodronate 1600mg for 2-3 years

Hadjii 2016 Ann Oncol; EBCTCG 2015 Lancet; Dhesy-Third 2017 J Clin Onc; O’Carrigan 2017 Cochrane Database

NICE evidence summary (ES15) 2017. Early breast cancer (preventing recurrence and improving survival): adjuvant bisphosphonates
Reduction in Skeletal Related Events (SREs) – Breast cancer

For women with known bone metastases

• Bisphosphonates reduce the risk of developing SREs by 14% (oral or IV compared to placebo or no bisphosphonate).
• Denosumab reduced the risk of developing a SRE compared with bisphosphonates by 22%.

O’Carrigan 2017 Cochrane Database
Reduction in Skeletal Related Events (SREs) – Prostate cancer

- NICE does not recommend bisphosphonates for the prevention of bone metastases in men with prostate cancer OR to prevent or reduce the complications of bone metastases in men with hormone-relapsed prostate cancer
- NICE does not recommend denosumab for preventing complications that result from prostate cancer spreading to the bone

Reduction in Skeletal Related Events (SREs) – Myeloma

- Cochrane review updated from 2012
- 24 studies
- Bisphosphonates reduce vertebral fractures and SREs

Mhaskar (2017) Cochrane Database
Reduction in SREs – other solid tumours

• Evidence limited for individual cancers
• Bisphosphonates and denosumab effective at reducing SREs in lung cancer, renal cell cancer and other solid tumours
• Expected survival should be > 3 months
• Both NICE approved

Which drug and how often?

• Myeloma – no evidence of superiority of any one bisphosphonate  
  Mhaskar (2017) Cochrane Database

• Breast cancer – Pamidronate, Zolendronic acid and Denosumab equally effective

• Zolendronic acid effective given 12 weekly

• Denosumab 4 weekly costs 100 x Zolendronic acid 12 weekly

Reduction in SREs – unanswered questions

Continuous or intermittent dosing?
Who needs 12 weekly and who needs 4 weekly dosing?
Who needs bisphosphonates and who will be better treated by Denosumab?
Pain control

- 15 studies demonstrating “pain relief well demonstrated” for bisphosphonates and a single study demonstrating effectiveness of denosumab
Pain control

• Systematic review of 43 studies within EAPC guidelines project.  
  Porta-Sales (2017) Pall Med

• 22/28 (79%) of the placebo-controlled trials on bisphosphonates found no analgesic benefit.

• None of the Denosumab studies assessed pain relief directly.  
  Porta-Sales (2017) Pall Med

• Excluding clodronate/etidronate studies – 8/14 (57%) analgesic benefit
Pain control

• Breast cancer - bisphosphonates appear to reduce bone pain compared to placebo or no bisphosphonate
  O’Carrigan 2017 Cochrane Database

• Bisphosphonates for pain relief may be considered for men with hormone-relapsed prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed.
  NICE (2014) Prostate cancer; diagnosis and management

• Myeloma - Use of bisphosphonates reduces pain
  Mhaskar (2017) Cochrane Database
Bisphosphonates - Adverse effects

• Pyrexia and flu-like syndrome
• Fatigue
• Headache
• Anxiety
• Hypertension
• Anaemia
• Thrombocytopenia
• Cough

• Arthralgia
• Myalgia
• Bone pain
• Hypocalcaemia
• Hypomagnesaemia
• Hypophosphataemia
• Osteonecrosis of the jaw
• Atypical femoral fractures
• Renal impairment
Adverse effects - updates

• MHRA/CHM advice: Denosumab: minimising the risk of osteonecrosis of the jaw; monitoring for hypocalcaemia—updated recommendations (September 2014) and Denosumab: osteonecrosis of the jaw—further measures to minimise risk (July 2015)

• MHRA/CHM advice: Denosumab: reports of osteonecrosis of the external auditory canal (June 2017)

• MHRA/CHM advice: Denosumab (Xgeva®) for giant cell tumour of bone: risk of clinically significant hypercalcaemia following discontinuation (June 2018)

• MHRA/CHM advice: Denosumab (Xgeva®) for advanced malignancies involving bone: study data show new primary malignancies reported more frequently compared to zoledronic acid (zoledronate) (June 2018)
Any questions?