

Use of bone-targeted agents in oncology

Bone metastases from solid tumors

- Introduction
 - Patients with bone metastasis are at risk for skeletal-related events.
 - Bisphosphonates and denosumab inhibit bone resorption. They relieve bone pain, prevent pathological fractures, and may have antitumor effects.
- Indication: all patients with bone metastases **EXCEPT**
 - Castration-sensitive prostate cancer
 - Poor dental status and/or refuse necessary dental care
 - Short life expectancy (<3mo)
- Potential adverse effects:
 - Hypocalcemia
 - Osteonecrosis of the jaw (especially after long-term use; about 1%/yr)
R/ stop BTA, refer to stomatologist
 - (atypical subtrochanteric fractures)
 - Bisphosphonates: renal insufficiency
- Before start:
 - Start Ca-vitD substitution. Correct pre-existing deficiencies if necessary
 - Dentist check & teeth extraction when necessary
 - Education on continued use of Ca-vitD to prevent deficiencies, importance of dental care, good fit of prosthesis if any, and alarm symptoms of osteonecrosis of the jaw. No invasive dental care is allowed without prior consultation.
 - CIVARS Xgeva
- PREFERRED: Denosumab 120mg SC
 - Q4w for first 4 times, then q3m
 - RANK ligand inhibitor which rapidly suppresses bone resorption.
 - Upon discontinuation, rapid rebound bone resorption occurs. In osteoporosis, this is associated with an increased vertebral fracture risk from 7mo after last dose. In cancer patients, the risk is unknown.
 - In case of persistent deep oncological response with limited bone metastases, consider stopping after 2 yrs. Upon stop, administer single dose of zoledronate to prevent excess vertebral fractures.
 - High-quality evidence to support extended dosing is lacking (REDUSE trial ongoing), but q12w is reasonable at pt request (Clemons et al, Eur J Cancer 2020). If pause >6months, offer single dose of zoledronate.
- Alternative: Zoledronic acid 4mg q4w IV.
 - *Bisphosphonates, which are pyrophosphate analogues, are ingested by osteoclasts at active bone remodeling sites and cause cell death. They accumulate in the bone and have a prolonged duration of action after discontinuation.*
 - *After 3-6 months, switching to extended dosing q12w is not inferior (ZOOM, OPTIMIZE-2)*
 - *In case of persistent deep oncological response with limited bone metastases, consider stopping after 2 yrs.*

Breast cancer, adjuvant setting

- Indication: Post-menopausal women or pre-menopausal with GnRH analogues, at significant risk of recurrence
- PREFERRED: zoledronate 4mg IV once.

Osteoporosis

- Risk: hormonal deprivation increases risk of osteoporosis
 - o Aromatase inhibitors, ovarian suppression or oophorectomy in breast cancer
 - o Androgen deprivation therapy or orchidectomy in prostate cancer
 - o Early menopause or male hypogonadism after chemotherapy (esp. platinum, antimetabolites, taxanes) or oophorectomy/orchidectomy: young breast, testicular, sarcoma etc survivors.
- Prevention & detection: chronic hormonal deprivation treatment
 - o Exercise, VitD substitution and calcium-enriched diet or calcium substitution
 - o Offer bone densitometry at start in patients with risk factors: >65yrs, smoking, BMI >24, history of fragility fracture above age 50, family history of hip fracture, glucocorticoid >6mo, excess alcohol, chronic liver disease, malabsorption, renal insufficiency
 - o Perform bone densitometry every 2 years
 - o Extended reimbursement for prostate cancer: denosumab 60mg (Prolia) q6mo if hip T-score ≤ 1
- Non-curative setting
 - o Ca-vitD substitution and bone densitometry based on individual risk factors and life expectancy. To consider especially in hormone sensitive breast cancer and castration-sensitive prostate cancer.
- Survivors
 - o Screen for testosterone deficiency in males (morning lab, 1x/yr) and early/premature menopause (anamnesis) in woman <45yr after hormonal deprivation or chemotherapy
 - o In case of hypogonadism:
 - Exercise, VitD substitution and calcium-enriched diet or calcium substitution
 - Bone densitometry & follow up bone densitometry as advised for the general population. For flowchart, see Sanchez-Rodriguez et al. in [The Belgian Bone Club 2020 guidelines for the management of osteoporosis in postmenopausal women](#).
- Treatment
 - o Standard: zoledronate 5mg IV q12mo
 - Reimbursed for 3 years if:
 - Vertebral fracture with $\geq 25\%$ reduction and $\geq 4\text{mm}$ documented in protocol
 - Hip fracture
 - T-score ≤ 2.5
 - Re-evaluation with bone densitometry 1 year after the 3rd administration or earlier if fracture. Bisphosphonates can be paused, “drug holiday”, which can be then monitored by the GP with bone turnover parameters.
 - o Very high fracture risk: romosozumab 210mg q4w

- Treatment for 1 year, then to be followed with bisphosphonate or denosumab.
- Reimbursed for prescription by rheumatologist if:
 - Post-menopausal ...
 - ... **AND any of**
 - Hip fracture
 - Wrist fracture ≥ 75 yr
 - Vertebral fracture with $\geq 25\%$ reduction and ≥ 4 mm documented in protocol
 - ... **AND any of**
 - T-score ≤ 2.5
 - Vertebral fracture with $\geq 25\%$ reduction and ≥ 4 mm documented in protocol
- Fracture risk without reimbursement of zoledronate: oral alendronate
 - Hormonal deprivation therapy and T-score ≤ 2
 - Hormonal deprivation therapy with ≥ 2 risk factors (see above)
 - Post-menopausal woman with fragility fracture
 - => Re-evaluation with bone densitometry after 5 years or earlier if fracture.