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Bone Health and the Cancer Patient

Description: The purpose of this PQI is to highlight the importance of bone health in cancer patients and to discuss monitoring and treatment of cancer-related bone loss. This includes the prevention of skeletal-related events (SREs) via administration of bone targeting agents (BTAs).

Background: Risk factors for cancer-related bone loss include prolonged hormone therapy, chemotherapy-induced early menopause, oophorectomy, glucocorticoid use, and certain cytotoxic agents. Additionally, bone metastases are a major cause of pain and morbidity for patients with metastatic cancer. The most common malignancies that metastasize to bone include multiple myeloma, as well as breast, prostate, lung, and kidney cancers. Bone loss is driven by tumor-mediated osteoclast activation, especially through receptor activator of nuclear factor kappa-B ligand (RANKL) overexpression, which leads to increased resorption and osteolytic lesions. BTAs including bisphosphonates and denosumab are used in cancer patients to reduce SREs, decrease pain, and improve quality of life.[1,2,3]

PQI Process:

1. Assess patients for risk of bone loss or SRE[4]
    - DEXA scan is gold standard
    - May use a risk assessment tool (eg, the WHO Fracture Risk Assessment Tool [FRAX]) to quantify the risk estimates for osteoporotic fracture in adult patients with nonmetastatic cancer[2]
    - High risk groups: fragility fracture present (e.g., distal radius fracture, hip fracture, any compression fracture); patients receiving aromatase inhibitors (AI), androgen deprivation therapy (ADT), or glucocorticoids
    - Patients with non-metastatic cancer who are prescribed a drug that causes bone loss should be offered bone mineral density testing every 2 years[2]
2. Calcium and Vitamin D Supplementation[4]
    - Calcium dosing recommendations for the prevention of bone loss and osteoporosis in cancer patients:
        - Females/males ages 19-50 = 1000mg daily
        - Females age 51 or older = 1200mg daily
        - Males age 51-70 = 1000mg daily
        - Males > 70 or older = 1200mg daily
    - Vitamin D levels should be assessed for patients to determine dose[3,4]
        - Goal serum 25-hydroxyvitamin D level = 30-60 ng/mL

Table 1. Vitamin D Replacement Therapy Guideline[3]

	Replacement Therapy x 4 Months & Recheck		Maintenance Therapy When Level 30-60 ng/mL
25(OH) D Level (ng/mL)	Ergocalciferol Vitamin D_2 (requires prescription)	Cholecalciferol Vitamin D_3 (OTC)	Cholecalciferol Vitamin D_3 (OTC)
<10	50,000 IU orally **once** weekly	-	2000 IU/d
10-20	-	2000 IU/d	2000 IU/d
20-30	-	1000 IU/d	1000 IU/d
>30	Continue patient's current regimen for all therapies		

25(OH) D: serum 25-hydroxyvitamin D

3. Bisphosphonate therapy: Zoledronic acid and Pamidronate[5]

- Indications: bone metastases from solid tumors, multiple myeloma
  - Off-label: bone loss associated with aromatase inhibitor therapy in postmenopausal patients, bone loss associated with androgen deprivation therapy
- Monitor renal function and adjust dose per manufacturer recommendations
- Osteonecrosis of the jaw (ONJ) can occur. Patients should receive comprehensive dental exams and appropriate dentistry prior to starting bisphosphonate therapy.
  - Avoid elective invasive dental procedures (tooth extraction or oral surgery) during therapy. Therapy should be held if dental procedures are necessary.
- Bisphosphonates are known to cause hypocalcemia; therefore, patients should receive adequate calcium and vitamin D supplementation (see dosing recommendations above).
- Common adverse effects may develop within 24-48 hours following administration and include fevers, flu-like symptoms, nausea, fatigue, and electrolyte abnormalities (more common with IV than with oral)
  - Administer acetaminophen to mitigate acute phase reaction (fever, myalgia, fatigue)
- Consider de-escalating zoledronic acid from q4 weeks to q12 weeks in stable patients after 3–6 months (see Table 2)[2,6]

Table 2. Comparison of trials evaluating every 4 weeks vs 12 weeks administration of zoledronic acid[7]

Study Name	Inclusion Criteria	Prior Bisphosphonate Use	Outcomes Assessed	Significant Difference in SREs	Renal Dysfunction & ONJ
ZOOM (Amadori et al., 2013)	Women with BMC	Yes (12–15 months every 3–4 weeks)	SREs, time to first SRE, bone pain, safety	No (22.1% vs 18.3%, p = 0.912)	Renal AEs: 1 (q12w) vs 2 (q4w); ONJ: 4 (q12w) vs 3 (q4w)
CALGB 70604 (Himelstein et al., 2017)	BMC, ≥18 yrs, ECOG 0–2; excluded prior IV BP use	No	≥1 SRE, bone pain, ECOG status, ONJ	No (p = 0.50)	Safety data for renal and ONJ not reported
OPTIMIZE-2 (Hortobagyi et al., 2017)	Women with MBC; ECOG ≤2, life expectancy ≥1 yr	Yes (11–15 months every 3–4 weeks)	≥1 SRE, time to first SRE, safety	No (SRE: 44 vs 47, not significant)	Renal AEs: 19 (q4w) vs 16 (q12w); ONJ: 2 cases (q12w)

BMC, bone metastatic cancer; BP, bisphosphonate; MBC, metastatic breast cancer

4. RANK-L therapy: Denosumab[8]

- Indications: bone metastases from solid tumors, giant cell tumor of the bone, multiple myeloma, osteoporosis/bone loss
  - Off-label: prevention of glucocorticoid-induced osteoporosis
- Adverse reactions occurring ≥ 20% of oncology patients include hypophosphatemia, hypocalcemia, diarrhea, nausea, anemia, asthenia, fatigue, back pain, and dyspnea.
- Preferred over bisphosphonates in patients with renal dysfunction.
  - Monitor patients with renal dysfunction closely for hypocalcemia and hypophosphatemia.
- ONJ can occur and patients should receive comprehensive dental exams and appropriate dentistry prior to starting therapy.
- Two different strengths and dosing schedules that are not interchangeable: 60mg SubQ every 6 months (osteoporosis) vs 120mg SubQ every 4 weeks (bone metastases)
- Rebound osteolysis leading to vertebral fractures has been documented upon discontinuation of denosumab therapy; NCCN recommends administration of at least one dose of bisphosphonate

(i.e., zoledronic acid 4 mg or 5 mg) post completion of denosumab therapy to prevent rebound fracture[2,3]

Table 3. Dose and frequency of BTAs for various indications[3]

		Zoledronic Acid		Denosumab	
Indication		Zometa® (4mg)	Reclast® (5mg)	Prolia® (60mg)	Xgeva® (120mg)
Reduction in SREs due to advanced cancer involving the bone	Bone metastases (monthly)	X	-	-	X
	Hypercalcemia	X	-	-	X
	Multiple myeloma (monthly)	X	-	-	X
Reduction in bone loss	AI-induced bone loss	X+	-	X++	-
	ADT-induced bone loss	X	-	X++	-
	Glucocorticoid therapy (yearly)	-	X	-	-

+every 3 months or yearly
++every 6 months

Patient-Centered Activities:

- Provide education to the patient on bone modifying treatment including dosing, administration and side effects to expect.
- Educate the patient to report any new or worsening symptoms including bone pain to the provider.
- Educate on the importance of good oral hygiene and dental checkups and report any new jaw pain or swelling.
- Encourage lifestyle modifications to support healthy bones
    - At least 30 minutes per day of moderate physical activity and lifestyle modifications to increase muscle mass, strength, and balance as well as bone strength.
    - Reduce tobacco use and high alcohol consumption.
- Inform patient to notify provider if pregnant or plan to become pregnant

Supplementary Material

	Zoledronic Acid	**Pamidronate**	**Denosumab**
Typical Dose and Schedule	4mg IV over 15-30 minutes every 4 weeks	60-90 mg IV over 2 to 6 hours every 4 weeks	120mg SubQ every 4 weeks
Clearance	Renal *Dose adjust when used for the prevention of SREs	Renal *Dose adjust when used for the prevention of SREs	No renal adjustment *Not studied in CrCl < 30 mL/min *Monitor patients with renal dysfunction for hypocalcemia and hypophosphatemia

	Diagnosis	Treatment & Dosing	Duration	Clinical Pearls
Breast Cancer	**EBC high-risk AI-related bone loss**	Zoledronic acid 4 mg IV q6 months *(preferred)* or Zoledronic acid 5 mg IV annually Denosumab 60 mg SC q6 months¥	~3-5 years *(optimal duration unclear; reassess after 3 years)*	Prevent bone loss only; recurrence benefit minimal/unclear. Guidelines support denosumab use for bone health, not recurrence.
	MBC (bone metastases)	Zoledronic acid 4 mg IV q12 weeks Pamidronate 90 mg IV q3-4 weeks Denosumab 120 mg q4 weeks	Data support up to 2 years; longer duration unproven but may provide benefit	Supplement with Ca^{2+} 1200–1500 mg/day + Vitamin D_3 400–800 IU/day Use bisphosphonates with systemic therapy (chemotherapy or endocrine therapy) in MBC patients with ≥3-month life expectancy to prevent SREs. Denosumab is superior to zoledronic acid in delaying SREs but carries higher risk of hypocalcemia and ONJ. No bone-modifying agent has demonstrated survival benefit, used for palliation, improve QoL and SRE prevention.
Prostate Cancer	**CSPC (ADT-related bone loss)**	Zoledronic acid 5 mg IV annually Denosumab 60 mg SC q6 months Alendronate 70 mg PO weekly *(home Rx)*	No defined duration; consider drug holiday after 3–5 years; reassess if BMD declines or fracture occurs	Initiate pharmacologic treatment if T-score –1.0 to –2.5 and FRAX ≥3% (hip) or ≥20% (major). Avoid osteoclast inhibitors for SRE prevention in CSPC but may be used for bone loss prevention.
	mCRPC (bone metastases)	Zoledronic acid 4 mg IV q12 weeks Denosumab 120 mg SC q4 weeks	Continue while metastatic disease is present; reassess at 2 years	Denosumab is more effective in delaying SREs than zoledronic acid but increases risk of ONJ and hypocalcemia.
Multiple Myeloma	**Myeloma-related bone disease**	Zoledronic acid 4 mg IV q4 weeks *(preferred)*	Up to 2 years; reassess based on response	All patients on active therapy should receive bone-modifying agents.

		Pamidronate 90 mg IV monthly *(preferred)* Denosumab 120 mg SC q4 weeks		If considering extended interval dosing, continue with denosumab q6 months or switch to bisphosphonate to prevent rebound fractures.
Other Cancers	**Bone metastases (solid tumors)**	Zoledronic acid 4 mg q3-4 weeks *(may extend to q12 week dosing in stable/responsive disease; further extending to q6-12 months may be considered based on osteoporosis recommendations)* Denosumab 120 mg SC q4 weeks	~2 years; optimal duration uncertain	Applicable across solid tumors with bone metastases. Used for palliation and SRE prevention.

Early-Stage Breast Cancer (EBC) • Metastatic Breast Cancer (MBC) • Aromatase Inhibitor (AI) • Castrate Sensitive Prostate Cancer (CSPC) • Metastatic Castrate Resistant Prostate Cancer (mCRPC) • Androgen Deprivation Therapy (ADT) • ¥If premenopausal on ovarian suppression with osteopenia only or postmenopausal on AI therapy.

References:

1. Van Poznak C, Temin S, Yee GC, et al. American Society of Clinical Oncology Endorsement of the Cancer Care Ontario Guideline on Bone Health and Bone-Targeted Agents in Breast Cancer. J Clin Oncol. 2021.
2. Shapiro C, et al. Management of Osteoporosis in Survivors of Adult Cancers With Nonmetastatic Disease: ASCO Clinical Practice Guideline. JCO 37, 2916-2946(2019).
3. DOI:10.1200/JCO.19.01696
4. ESMO Clinical Practice Guidelines. Bone Health in Cancer Patients. European Society for Medical Oncology, 2020.
5. Gralow, J. R. et al. NCCN Task Force Report: Bone Health in Cancer Care. J. Natl. Compr. Canc. Netw. 11, S-1-S-50 (2013).
6. Calcium Supplements | Memorial Sloan Kettering Cancer Center. https://www.mskcc.org/cancercare/patient-education/calcium-supplements. Accessed 11/10/2022.
7. Zometa (zoledronic acid) [package insert] Stein, Switzerland : Novartis Pharma; 2014
8. Anderson K, Ismaila N, Kyle RA. Role of Bone-Modifying Agents in Multiple Myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update Summary. J Oncol Pract. 2018 Apr;14(4):266-269. doi: 10.1200/JOP.17.00013. Epub 2018 Mar 8. PMID: 29517956.
9. Yang M, Yu X. Management of bone metastasis with intravenous bisphosphonates in breast cancer: a systematic review and meta-analysis of dosing frequency. Support Care Cancer. 2020 Jun;28(6):2533-2540. doi: 10.1007/s00520-020-05355-7. Epub 2020 Feb 14. PMID: 32060705.
10. Xgeva (denosumab) [package insert] Thousand Oaks, CA: Amgen; Revised 2013
11. Anderson K, Ismaila N, Flynn PJ, et al. Role of Bone-Modifying Agents in Multiple Myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. Mar 10 2018;36(8):812-818. doi:10.1200/JCO.2017.76.6402
12. Terpos E, Morgan G, Dimopoulos MA, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. J Clin Oncol. Jun 20 2013;31(18):2347-57
13. Amadori D, Aglietta M, Alessi B, et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomized, non-inferiority trial. Lancet Oncol. Jun 2013;14(7):663-70. doi:10.1016/s1470-2045(13)70174-8