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Palliative Care Pharmacy
PHAST PHACT

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TODAY'S TOPIC:

Bone Modifying Agents for Breast Cancer
2017 Updated Guidelines

Background:

Metastases to bone are a common site for many types of solid tumors. Bone metastases cause substantial morbidity, including the need for radiation or surgery to bone for symptoms, fractures, hypercalcemia of malignancy, and spinal cord compression. Osteoclast inhibitors (also called bone-modifying agents (BMAs)) such as bisphosphonates and denosumab significantly reduce the frequency of skeletal-related events (SREs) in patients with bone metastases from a wide variety of cancer types. Osteoclast inhibition has become an important component of managing patients with bone metastases to reduce the frequency and delay the onset of SREs. While the frequency of SREs in patients not treated with an osteoclast inhibitor has been explored, it is important to state that improvements anticancer treatments in recent years may have also reduced the incidence of SREs.

The American Society of Clinical Oncology (ASCO) have published numerous guidelines on the role of BMAs in metastatic breast cancer since 2000. They recently updated their guidelines in 2017.

Importance:

Palliative care providers often care for patients with breast cancer. They should be aware of all oncology guidelines regarding the care for these patients.

The Article:

- J Clin Oncol. 2017 Dec 10;35(35):3978-3986.
  Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update.

Palliative Care Pharmacy Team:

Clinical Pharmacy Specialist:
Jenn Pruskowski, PharmD, BCPS, BCGP, CPE
pruskowskija@upmc.edu

If you have a topic you would like the pharmacy team to answer, please send your suggestions to: pruskowskija@upmc.edu

- Purpose: To update, in collaboration with Cancer Care Ontario (CCO), key recommendations of the American Society of Clinical Oncology (ASCO) guideline on the role of bone-modifying agents (BMAs) in metastatic breast cancer. This focused update addressed the new data on intervals between dosing and the role of BMAs in control of bone pain
- Methods: A joint ASCO-CCO Update Committee conducted targeted systematic literature reviews to identify relevant studies.
- Recommendations:
    - As recommended in the 2011 version of the ASCO BMAs guideline, patients with breast cancer who have evidence of bone metastases should be treated with BMAs. One BMA is not recommended over another. If patients are treated with zoledronic acid, 4 mg intravenously administered over no less than 15 minutes, dosing options are every 12 weeks or every 3 to 4 weeks
    - The analgesic effects of BMAs (denosumab, pamidronate, or zoledronic acid) are modest, and they should not be used alone for bone pain. The Panel recommends that the current standard of care for supportive care and pain management be applied. This can include analgesia, adjunct therapies, radiotherapy, surgery, systemic anticancer therapy, and referral to supportive care and pain management. Evidence of a clinically meaningful benefit is insufficient to support the use of one BMA over another. Further research is needed on this clinical question.
- Conclusion: "Additional information is available at www.asco.org/breast-cancer-guidelines and www.asco.org/guidelineswiki ."
- *Discussion:* These guidelines were updated due to the phase III studies of breast cancer and dosing intervals for zoledronic acid (see here: JAMA. 2017 Jan 3;317(1):48-58.)

So… What does this all mean Jenn?

- Although BMAs are often initiating and continued by oncologists, if you are caring for a patient with breast cancer, be sure they are receiving BMAs at least every 12 weeks. These therapies should be continued indefinitely in the absence of excessive toxicity and as long as treatment is consistent with both the patient's treatment goals
- According to these guidelines, providers can choose between zoledronic acid and denosumab. Here are some important pharmacotherapy factors to consider:

Parameter	Zoledronic Acid	Denosumab
Safety	Contraindicated in patients with a CrCl <35mL/min	None
Tolerability	Hypocalcemia	Hypocalcemia (especially in patients with CrCl

	Reduce in renal impairment Osteonecrosis of the jaw (ONJ) – prevalence ~2% - NNH ~2,000-60,000	<30mL/min) – *may be more prevalent* Osteonecrosis of the jaw (ONJ) - *may be more prevalent*
Efficacy	A patient-level meta-analysis of these three phase III trials comparing zoledronic acid with denosumab for metastatic bone disease concluded that denosumab was superior to zoledronic acid in reducing the risk of a first on-study SRE (hazard ratio [HR] 0.83, 95% CI 0.76-0.90) and in delaying the time to a first SRE or hypercalcemia of malignancy Denosumab has also demonstrated modest but statistically significant quality of life benefits over zoledronic acid	
Price	UPMC inpt price/dose: $47.00	UPMC inpt price/dose: $1761.35
Simplicity	Dosed q3-4w or q12w – IV infusion Should administered Ca2+ and VitD as necessary	Administered q4w – subcutaneous infusion Should administered Ca2+ and VitD as necessary

Key: NNH: number-needed-to-harm; CrCl: creatinine clearance

- So as you can see, due for price and other considerations, zoledronic acid should be considered first line
- In regards to Ca2+ and VitD: if a patient's dietary intake is inadequate an average of a least 1200mg Ca2+ and 800-1000 IU VitD should be taken daily
- The other important point is that BMAs should not be used alone for bone pain. Consider other therapies such as NSAIDs and steroids. See previous PCP Phast Phacts for more information regarding these agents

Geriatric Considerations:

- Special considerations for older adults have not been established
- Continue to monitor hydration levels and renal function (as above)

Stay tuned for future PCP Phast Phacts on bone-modifying agents!

CLINICAL PEARL:
Bone-modifying agents, first line being zoledronic acid, should be administered at least every 12 weeks to patients with breast cancer, and other analgesic agents should also be considered for bone pain.