American Society of Clinical Oncology Executive Summary of the Clinical Practice Guideline Update on the Role of Bone-Modifying Agents in Metastatic Breast Cancer

IDENTITY

Citation

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PURPOSE

Objective

· To update the recommendations on the role of bone-modifying agents in the prevention and treatment of skeletal-related events (SREs) for patients with metastatic breast cancer with bone metastases

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METHODOFDEVELOPMENT

Rating Scheme

Evidence Quality Rating Scheme

Recommendation Strength Rating Scheme

Qualifying Statement

TARGETPOPULATION

women with bone metastases from breast cancer:

Inclusion Criterion

Exclusion Criterion

KNOWLEDGE COMPONENTS

DEFINITIONS

RECOMMENDATION: Indications and time of initiation

Conditional: For breast cancer patients who have evidence of bone destruction on plain radiographs, IV pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended. Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction, but normal plain radiographs, is considered reasonable by Panel consensus based on the □?ndings in women with lytic or mixed lytic/blastic changes on plain radiographs. {Rec_1:Cond_ 1 }

Decision Variable: breast cancer patients who have evidence of bone destruction on plain radiographs

Value: true

Action: IV pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended

Evidence Quality: Strong (primarily phase III RCTs)

Logic: If breast cancer patients have evidence of bone destruction on plain radiographsORhave an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction, but normal plain radiographs Then deliver IV pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks

RECOMMENDATION1: Indications and time of initiation/extraskeletal mets

Conditional: Starting bone-modifying agents in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, CT scans, or MRI is not recommended outside of a clinical trial. {Rec_2:Cond_ 2 }

Decision Variable: women with only an abnormal bone scan but without evidence of bone destruction on radiographs, CT scans, or MRI even in the presence of other extraskeletal metastases

Value: true

Action: Do not start bone-modifying agents

Logic: If women have only an abnormal bone scan NOT evidence of bone destruction on radiographs, CT scans, or MRI, even in presence of extraskeletal metastasesThen do not start bone-modifying agents

RECOMMENDATION2: Renal safety concerns

Conditional: In patients with a calculated serum creatinine clearance > 60 mL/min, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid administration is required. {Rec_4:Cond_ 4 }

Decision Variable: patients with a calculated serum creatinine clearance > 60 mL/min

Value: true

Action: do not change dosage, infusion time, or interval of pamidronate or zoledronic acid administration

Logic: If In patients have a calculated serum creatinine clearance > 60 mL/minThen do not change in dosage, infusion time, or interval of pamidronate or zoledronic acid administration

RECOMMENDATION3: Renal safety concerns 2

Conditional: The packet insert of zoledronic acid provides guidance for dosing when baseline serum creatinine clearance is > 30 and < 60 mL/min. Infusion times < 2 hours with pamidronate or < 15 minutes with zoledronic acid should be avoided. {Rec_3:Cond_ 3 }

Decision Variable: If patient taking zoledronic acid and baseline serum creatinine clearance is > 30 and < 60 mL/min

Value: true

Action: use packet insert of zoledronic acid for dosing guidance

Logic: If Patient's baseline serum creatinine clearance is > 30 and < 60 mL/minThen refern The packet insert of zoledronic acid dosing guidance

RECOMMENDATION4: Renal safety concerns 3

Imperative: The Panel recommends that serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid, in accordance with FDA-approved labeling. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly. {Rec_5:Imp_ 5 }

Directive: Monitor serum creatinine prior to each dose of pamidronate or zoledronic acid, in accordance with FDA-approved labeling. Regularly monitor serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin.

RECOMMENDATION: Renal safety concern 4

Conditional: Monitor for hypocalcemia in patients with impaired creatinine clearance. {Rec_6:Cond_ 6 }

Decision Variable: patients with impaired creatinine clearance

Value: True

Action: Monitor for hypocalcemia

Logic: If patients have impaired creatinine clearance Then Monitor for hypocalcemia

RECOMMENDATION: ONJ

Conditional: The Update Committee concurs with the revised FDA label for zoledronic acid and pamidronate and the FDA label for denosumab and recommends that all patients with cancer receive a dental examination and necessary preventive dentistry prior to initiating therapy with inhibitors of osteoclast function unless there are mitigating factors that preclude the dental assessment. {Rec_11: Cond_ 11 }

Decision Variable: mitigating factors

Value: not

Action: dental examination and necessary preventive dentistry prior to initiating therapy with inhibitors of osteoclast function

Logic: If NOT mitigating factors Then patients should recived a dental examination and necessary preventive dentistry prior to initiating therapy with inhibitors of osteoclast function

Imperative: While receiving inhibitors of osteoclast function, patients should maintain optimal oral hygiene and, if possible, avoid invasive dental procedures that involve manipulation of the jaw bone or periosteum. {Rec_11:Imp_ 11 }

Directive: maintain optimal oral hygiene and avoid invasive dental procedures that involve manipulation of the jaw bone or periosteum

RECOMMENDATION: Optimal duration

Imperative: The Panel suggests that once initiated, IV bisphosphonates be continued until evidence of substantial decline in a patient's general performance status. {Rec_10:Imp_ 10 }

Directive: continue IV bisphosphonates until evidence of substantial decline in a patient's general performance status

Evidence Quality: There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events. There are no prospective clinical RCT data to support the continuation of bone-modifying agent therapy beyond 1 year, especially for patients who are expected to survive longer than 1 year. There is a paucity of prospective data addressing long-term toxicities of bisphosphonates.

Flexibility: The Panel stresses that clinical judgment must guide what is a substantial decline.

RECOMMENDATION: The Panel recommends that the current standards of care for cancer bone pain management be applied at the onset of pain, in concert with the initiation of bone-modifying agent therapy. This is required by good clinical practice. The standard of care for pain management includes the use of nonsteroidal anti-inflammatory agents, opioid and

nonopioid analgesics, corticosteroids, adjuvant agents, interventional procedures, systemic radiopharmaceuticals, local radiation therapy, and surgery. Bone-modifying agents are an adjunctive therapy for cancer-related bone pain control and are not recommended as □?rst-line treatment for cancer-related pain. IV pamidronate or zoledronic acid may be of bene□?t for patients with pain caused by bone metastases and contribute to pain relief when used concurrently with analgesic therapy, systemic chemotherapy, radiation therapy, and/or hormonal therapy. Bone-modifying agents have been associated with a modest pain control bene□?t in controlled trials.

Conditional: IV pamidronate or zoledronic acid may be of bene□?t for patients with pain caused by bone metastases and contribute to pain relief when used concurrently with analgesic therapy, systemic chemotherapy, radiation therapy, and/or hormonal therapy {Rec_9: Cond_ 9 }

Decision Variable: patient has pain caused by bone metastases

Value: true

Action: give pain relief with IV pamidronate or zoledronic acid

Description: Approved types of pain relief analgesic therapy, systemic chemotherapy, radiation therapy, and/or hormonal therapy to use with IV bisphosphonates

Reason: Bone-modifying agents have been associated with a modest pain control bene□?t in controlled trials.

Logic: If patient has pain caused by bone metastases is [true]Then then clinician may give IV pamidronate or zoledronic acid

Imperative: current standards of care for cancer bone pain management be applied at the onset of pain, in concert with the initiation of bone-modifying agent therapy {Rec_9:Imp_ 9 }

Directive: Initiate cancer bone pain management according to current standards of care at the onset of pain, in concert with the initiation of bone-modifying agent therapy.

RECOMMENDATION: The use of biochemical markers to monitor bone-modifying agent use is not recommended.

Imperative: Do not use biochemical markers to monitor bone-modifying agent use {Rec_8:Imp_ 8 }

Reason: Although there have been several studies showing decreases in bone resorption or formation markers after administration of bone-modifying agents, no RCTs on biomarkers in this setting have been published that used SREs as a primary end point, and the studies' designs do not permit conclusions about the clinical utility of these markers.

Evidence Quality: Insufficient

ALGORITHM: