BONE HEALTH IN CANCER: Guidance for Physicians and Allied Health Care Professionals

Dr. Priya Manjoo, MBBS FRCPC Endocrinology and Metabolism,
Vancouver Island Health Authority, Victoria BC
Conflict of Interest: Amgen - Honoraria for educational symposia. Advisory boards
Dr. Negin Shahid, MD MSc FRCPC Radiation Oncology,
British Columbia Cancer - Victoria, Vancouver Island Health Authority
Conflict of Interest: None
Dr. Akshay Jain, MD FRCPC Endocrinology and Metabolism,
Fraser Health Authority, Surrey, BC
Conflict of Interest: Advisory board, Speaking honorarium and Clinical research participation- Amgen.
Dr. Kerstin Gustafson, MD FRCSC Gynecology,
Fraser Health Authority, Surrey, BC
Conflict of Interest: Advisory board, Speaking honorarium - Amgen.
Dr. Sue Purkiss, MD FRCPC Internal Medicine,
Provincial Health Services Authority, Vancouver, BC
Conflict of Interest: None
Dr. David Kendler, MD FRCPC Endocrinology and Metabolism,
Vancouver Coastal Health Authority, Vancouver BC
Conflict of Interest: consultancies, and/or speakers Bureau for Amgen, Sandoz, ZP Pharma.

We acknowledge the following BC Cancer health providers who generously offered their time and expertise as peer reviewers:
Dr. Stephen Chia, MD FRCPC Medical Oncology
British Columbia Cancer – Vancouver
Dr. Hamid Raziee, MD MHSc FRCPC Radiation Oncology
British Columbia Cancer – Kelowna
Dr. Jack Zheng, MD FRCPC Radiation Oncology
British Columbia Cancer - Abbotsford, Fraser Health Authority
Dr. Krista Noonan, MD FRCPC Medical Oncology
British Columbia Cancer – Surrey
Dr. Pamela Gardner, DMD, DABOM Oral Oncology/Dentistry
British Columbia Cancer – Vancouver
Dr. Malcolm Brigden, MD FRCPC Internal Medicine, Hematology
British Columbia Cancer – Kamloops Cancer Clinic
Dr. Francois Germain, MD FRCPC Radiation Oncology
British Columbia Cancer – Kelowna
Dr. Susan Balkwill, MD FRCPC Radiation Oncology
British Columbia Cancer – Surrey
Dr. Rona Cheifetz, MD Med FRCSC Hereditary Cancer Program
British Columbia Cancer – Vancouver
Dr. Dan Le, MD MHA, FRCPC Medical Oncology
British Columbia Cancer – Surrey
Dr. Christine Simmons, MD FRCPC Medical Oncology
British Columbia Cancer – Vancouver

TABLE OF CONTENTS

INTRODUCTION

The treatment of cancer has important implications for bone health. Clinicians treating cancer should be aware of the how cancer treatment affects the patient’s bone quality and risk of fracture.

In patients with non-metastatic cancer, both the disease itself, through an association with increased local and systemic inflammation, and its treatment can affect skeletal integrity. Systemic therapies for breast cancer and prostate cancer can additionally interfere with bone turnover, either through their effects on gonadal steroid hormone production or by inhibiting peripheral aromatization of testosterone into estrogen [1-3]. Metastatic bone disease can impair bone integrity leading skeletal-related events (SREs) which include pathological fracture, need for radiotherapy (RT) to bone, surgery to bone and nerve or spinal cord compression.

Patients should be informed of the availability of multidisciplinary interventions to reduce the risk of damage to the skeleton, and the treatments that reduce the risk of SREs in patients with bony metastases.

The management of bone health in patients with cancer builds on the management of osteoporosis in non-cancer patients which is addressed by the Osteoporosis Canada Clinical Practice Guidelines, as well as the guidelines published by the American Association of Clinical Endocrinologists, the Endocrine Society and the North American Menopause Society, There are additional factors that need to be considered when addressing bone health in cancer, including risk factors for osteoporosis, the type of cancer and presence or absence of bony metastases, as well as the use of systemic therapies (such as aromatase inhibitors, gonadotrophin-releasing hormone agonists and androgen deprivation therapy) which can impair bone health. Fall risk is especially important in making decisions about treatment as it is a strong contributor to the occurrence of fractures. If pharmacotherapy is recommended for fracture reduction, the choice of agent should take into account the patient’s preferences regarding route of administration, cost and burden of monitoring associated with the treatment, as well as the patient’s goals of care in the context of cancer treatment.

This document is intended to provide guidance to oncologists, endocrinologists, primary care physicians, and allied health care professionals who form part of the multidisciplinary cancer care team, on the management of bone health in cancer patients. This document also contains links to resources to inform management.

The pattern of referrals within a multidisciplinary team varies based on staffing and access to specialists. All patients should be educated about the effect of cancer treatment on their bone health as well as lifestyle measures to optimize bone health and reduce the risk of fractures. Referrals to bone

health specialists should be considered for further assessment and management as agreed upon by the patient and their care providers.

BONE HEALTH IN CANCER PATIENTS

I. ASSESSING BONE HEALTH IN PATIENTS BEING TREATED FOR CANCER

Q1. Which cancer patients require a bone mineral density (BMD) test?

- Patients on agents which suppress sex steroids are at risk of bone loss. All patients initiating gonadotrophin-releasing hormone (GnRH) agonists to suppress endogenous sex steroids, androgen deprivation therapy (ADT) or aromatase inhibitor (AI) therapy for prostate cancer or breast cancer respectively should have a baseline bone mineral density (BMD) test. Pre-treatment BMD testing facilitates timely preventive treatment to preserve bone health.

Q2. What blood tests are required in oncology patients prior to initiating fracture reduction therapy?

- Calcium, phosphate, creatinine, eGFR.
- Blood tests do not diagnose osteoporosis nor do they identify patients suitable for therapy. However, they are required to rule out other secondary causes of bone loss (such as myeloma, monoclonal gammopathy of undetermined significance (MGUS), primary hyperparathyroidism, hyperthyroidism, celiac disease anti-Tissue Transglutaminase IgA antibody (tTG-IgA) and vitamin D deficiency) and to ensure the safety and efficacy of osteoporosis therapy. These tests may be performed at the discretion of the care provider.

Q3. Which oncology patients require spine imaging for vertebral morphometry?

- Patients with significant height loss (greater than 2 cm measured height loss or greater than 4 cm historical height loss), those with unexplained severe back pain, patients with marked kyphosis, and patients with abnormalities on the DXA image suggestive of vertebral fracture should be considered for lateral thoracic and lumbar spine radiographs with specific instructions to the radiologist to identify vertebral fractures.
- Vertebral fractures and hip fractures are pathognomonic of clinical osteoporosis. Patients with vertebral fracture are at highest future fracture risk and require therapy regardless of Fracture Risk Assessment Tool (FRAX) score or BMD.

Q4. How do you evaluate fracture risk?

- Fracture Risk Assessment Tool (FRAX) and Canadian Association of Radiologists Osteoporosis Canada (CAROC) risk scores can identify patients at high risk of fracture based on osteoporosis-related risk factors which have been validated in large prospective population-based studies in postmenopausal women.

Q5. How do you evaluate fracture risk in patients being treated for cancer?

- FRAX and CAROC do not allow input of risks from ADT or AI; treatment decisions must be based on clinical risk factors and BMD data (see section 3).

II. GENERAL PRINCIPLES OF OSTEOPOROSIS MANAGEMENT

Q1. What are the aspects of lifestyle that should be encouraged to optimize bone health?

- Adequate nutrition and physical activity are prerequisites for improving and maintaining bone health and ensuring an optimal response to pharmacotherapy aimed at reducing fractures.

- **Calcium & Vitamin D.** Osteoporosis Canada recommends that adults over 50 or younger adults at high risk (with osteoporosis, multiple fractures, or conditions affecting vitamin D absorption) should receive 800 – 2,000 IU Vitamin D3 (https://osteoporosis.ca/vitamin-d/) and 1200 mg of elemental calcium daily (https://osteoporosis.ca/calcium/).

- **Vitamin and Mineral Supplements.** Other than Vitamin D, Health Canada states that most individuals can meet their vitamin and mineral needs through diet.

- **Protein.** In Canada, the current recommendation estimates protein requirements at 0.8 grams per kilogram of body weight per day, or accounting for between 10 to 35 percent of daily calories. (https://www.canada.ca/en/health-canada/services/nutrients/protein.html).

- **Caffeine and Salt.** Salt intake should be limited to 2300 milligrams (mg) per day. Healthy adults should consume no more than 400 mg of caffeine per day, or about three 8-oz cups (237 mL) of brewed coffee per day (no more than 2.5mg/kg). Caffeine intake recommendations are found at: https://www.canada.ca/en/health-canada/services/food-nutrition/food-safety/food-additives/caffeine-foods/foods.html.

- **Physical Activity.** Adults should accumulate at least 150 minutes of moderate-to-vigorous physical activity per week; participate in muscle strengthening activities at least twice a week and accumulate several hours of light physical activities per week. Adults aged 65 years and older should include physical activities that challenge balance. Patients can be directed to the Health Canada movement guidelines at: https://csepguidelines.ca/.

- **Smoking.** Health Canada recommends all smokers endeavor to quit or reduce tobacco intake. Helpful resources can be found at www.quitnow.ca and https://www.canada.ca/en/health-canada/services/smoking-tobacco/quit-smoking.html.

- **Fall prevention.** We have adapted recommendations from Sunnybrook Hospital (https://health.sunnybrook.ca/cancer/cancer-treatment-falling/). Cancer, and its treatments, increases the risk of fall. Research has found that falls occur in 30-50% of people with cancer over the age of 65. Recommendations to patient should include:

    - To wear footwear that has good support, low/no heels and a good tread, avoid wearing stocking/sock feet or going barefoot.
    - Review patient medications, including non-prescription drugs,that may predispose to falls. Patients should report drowsiness, dizziness, blurred vision, unsteadiness or falls.

- Consider falls risk at home and whether a home assessment with an occupational therapist would be advisable. Throw rugs, dim lighting and cluttered areas can increase falls risk.
- Consider installing equipment that can help prevent falls, particularly in the bathroom such as grab bars, and raised toilet seats.
- Consider use of an emergency response system.
- Consider the use of assistive devices. Canes, walkers and rollaters can provide support for people with balance issues or weakness in their legs.
- Exercise: Cardiovascular and resistance exercises can help increase muscular strength, flexibility and power, and can also improve balance.
- Most communities have fall prevention services for high risk patients.
- A list of contacts and patient resources in multiple languages can be found at: http://www.vch.ca/public-health/health-topics-a-z/topics/fall-prevention.

Q2. What are the therapies available for fracture reduction?

Anti-resorptive Agents	**Dosing**	**Route**	**Mechanism of Action**	**Pharmacare Coverage**
Bisphosphonates: (oral) ***Alendronate** ***Risedronate**	One tablet (alendronate 70 mg, risedronate 35 mg) once weekly	Oral	Bisphosphonates are internalized by osteoclasts causing them to apoptosis and thereby reducing bone resorption.	Special authority
Bisphosphonates: (intravenous) ***Zoledronic Acid**	5 mg annually	IV infusion		Special authority
***Denosumab**	60 mg every 6 months	Subcutaneous	Denosumab is a monoclonal antibody which blocks a protein RANK-L which is secreted and expressed by osteoblasts. This leads to reduced bone resorption	Special authority
Selective Estrogen Receptor Modulators (SERMS) ***Raloxifene**	60 mg tablet once daily	oral	**Selective Estrogen receptor modulators:** selectively bind to estrogen receptors, have an estrogen like agonist effect on bone and block resorption while having antagonist effect on breast and neutral effect on endometrial tissue	Special authority

*Pharmacare coverage may change and practitioners are encouraged to use the link to pharmacare to obtain the most current information on the coverage.

III. TREATMENT OF BONE HEALTH IN CANCER PATIENTS ON ENDOCRINE THERAPIES

Patients receiving endocrine therapies for the treatment of cancer (breast cancer and prostate cancer) experience accelerated bone loss and based on their risk factors for osteoporosis they may be offered medications to slow bone loss and reduce fractures. Guidelines for management of these patients are provided by the European Society of Medical Oncology (ESMO).

Q1. Which patients with cancer would benefit from fracture reduction therapy?

- Regardless of cancer therapy the following patients should be offered fracture reduction therapy.
    - Patients with a high risk of fracture based on FRAX or CAROC.
    - Patients with a prior history of fragility fractures especially recent fracture. Fragility fracture at any BMD may define clinical osteoporosis.
    - Patients with femoral neck, total hip, or lumbar spine bone density T-scores less than -2.5 should be offered antiresorptive therapy.

- Patients with cancer may already have one of the indications above that would support fracture reduction therapy. Patients receiving endocrine therapies are at higher risk of fracture but the FRAX and CAROC risk scores are limited in assessing fracture risk in this patient population.

- Patients who are receiving cancer endocrine therapies (aromatase inhibitor or androgen deprivation therapy), who have two clinical risk factors (shown above) or those who have a T score of < -2.0 should be offered antiresorptive therapy. The European Society for Medical Oncology guidelines [4] and the American Society of Clinical Oncology guidelines [5] provide evidence-based advice on the management of bone health in cancer patients receiving endocrine therapies.

- Denosumab is now approved for coverage by Pharmacare for the primary prevention of fractures in women being treated with aromatase inhibitors. The coverage is only available for 5 years after which patients should be counselled on either continuing denosumab or transitioning to another antiresorptive agent in order to prevent rapid bone loss that occurs after discontinuation of denosumab [6].

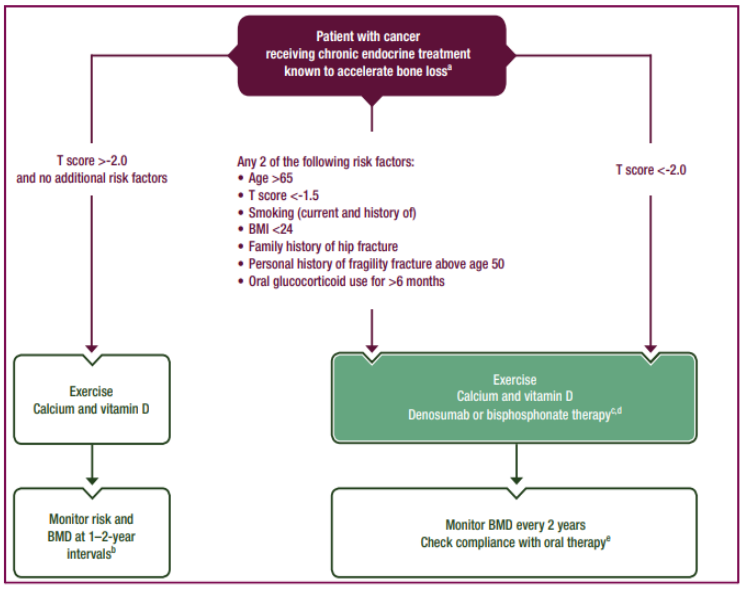

Figure 3. Recommended algorithm for managing bone health during cancer treatment.
ADT, androgen deprivation therapy; AI, aromatase inhibitor; BMD, bone mineral density; BMI, body mass index; DXA, dual X-ray absorptiometry; ONJ, osteonecrosis of the jaw.
[a] Include AIs and ovarian suppression therapy/oophorectomy for breast cancer and ADT for prostate cancer.
[b] If patients experience an annual decrease in BMD of ≥10% (or ≥4%–5% in patients who were osteopenic at baseline) using the same DXA machine, secondary causes of bone loss such as vitamin D deficiency should be evaluated and antiresorptive therapy initiated. Use lowest T score from spine and hip.
[c] Six-monthly intravenous zoledronate, weekly oral alendronate or risedronate or monthly oral ibandronate for the duration of endocrine treatment/for up to 5 years.
[d] Denosumab as first-line treatment followed by bisphosphonates (together for up to 5 years).
[e] Although ONJ is a very rare event with bone protection doses of antiresorptives, regular dental care and attention to oral health is advisable.
Adapted from Hadji et al. 2017[97] under a Creative Commons license. https://www.creativecommons.org/licenses/by-nc-nd/2.0/.

Figure 1. Coleman R, Bone health in cancer: ESMO Clinical Practice Guidelines[4].

IV. BONE TARGETED THERAPY IN PATIENTS WITH BONY METASTASES

Patients with cancer who have metastasis to the bone may benefit from treatment with higher doses of anti-resorptive therapy (denosumab 120 mg monthly or zoledronic acid 4 mg monthly or every 3 months) in order to reduce the risk of skeletal related events (SREs) [7]. Skeletal related events refer to pathologic fractures, nerve compression, requirement for radiation or surgery to bone, and hypercalcemia of malignancy. Therapeutic efficacy has been best demonstrated in castrate resistant prostate cancer and metastatic breast cancer patients, the clinical trials show benefit in limited numbers of patients with other solid tumor. In addition to monthly blood work to ensure adequate renal function and serum calcium, cancer patients on bone targeted therapy have a higher risk of osteonecrosis of the jaw than in osteoporosis patients on anti-resorptive therapy and require a dental screening prior to starting treatment.

Q1. What is the role of bone targeting agents (BTA) and which patients should be considered for BTA?

- SREs in patients with bony metastatic disease include pathologic fractures, nerve compression, requirement for radiation or surgery to bone, and hypercalcemia of malignancy.
- Such events significantly deteriorate patient quality of life, and result in increased healthcare expenditures.
- BTAs can reduce the risk of skeletal related events by up to 60% as compared to no treatment.
- BTAs complements therapy with radiation and anti-tumor strategies in patients at risk of skeletal related events.
- Patients who are candidates for BTAs include those with multiple bone metastases, and patients with prior skeletal related events.
- BTAs have demonstrated efficacy over a broad range of tumors metastatic to bone including multiple myeloma. Patients with castrate sensitive prostate cancer may have sufficient benefit from

androgen deprivation therapy on its own but should also be assessed and treated to protect bone health even if BTA are not required

Q2. What are the bone targeting agents available for use in BC?

There are three BTAs available, bisphosphonates (zoledronic acid and pamidronate) and denosumab are potent inhibitors of bone resorption. Denosumab 120 mg monthly has been shown to be more effective in delaying or preventing SREs in patients with bone metastases from solid tumors [8] (See table 2). Updated information regarding formulary access to medications can be found at https://pharmacareformularysearch.gov.bc.ca/Search.xhtml.

Table 2

Agent	Dose	Route	Pharmacare Coverage
*Denosumab	120 mg every 4 weeks	subcutaneous	Plan P
*Zoledronic acid	4 mg every 1-3 months	Intravenous	Plan P BCCA Formulary coverage for patients with high-risk breast cancer
*Pamidronate	90 mg every month	intravenous	Plan P Special authority for patients with bony metastases from cancer except for breast cancer.

*Pharmacare coverage may change and practitioners are encouraged to use the link to pharmacare to obtain the most current information on the coverage.

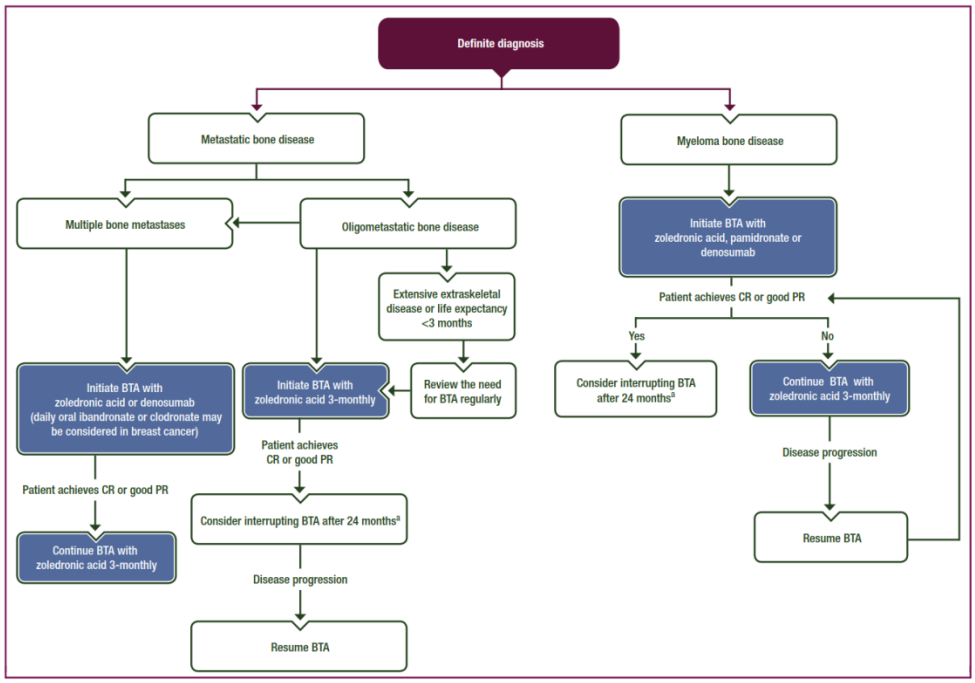

Figure 1. Algorithm for use of bone-targeted treatments for bone metastases and myeloma bone disease.
BTA, bone-targeted agent; CR, complete response; PR, partial response.
[a] See the recommendations about discontinuation of denosumab in the text.

Figure 2. Coleman R, Bone health in cancer: ESMO Clinical Practice Guidelines[4].

Q3. Why is it important that cancer patients with metastases have a dental screening to optimize oral health before exposure to IV bone targeting agents?

There is a risk of Medication Related Osteonecrosis of the Jaws (MRONJ) associated with all three BTAs: bisphosphonates (zoledronic acid and pamidronate) and denosumab. While MRONJ can occur spontaneously or as a result of poorly fitting dentures, dental extractions are the most common identifiable predisposing factor. For cancer patients exposed to BTAs, the risk of developing MRONJ after tooth extraction ranges from approximately 2 to 15 percent, Several studies report that among patients that develop MRONJ, tooth extraction is cited as a predisposing event ranging from 62 to 82 percent [9,10].

As there is no way to predict which patients will develop MRONJ, it is recommended that all cancer patients are referred to BC Cancer Oral Oncology/Dentistry for a screening prior to starting BTA therapy.

Treatment planning for patients at risk of developing MRONJ includes a thorough oral examination with radiographs to identify and manage both acute infection and sites of potential infection, Considerations during the clinical and radiographic assessment include patient motivation and access to regular dental care, tooth mobility, periodontal disease, broken and non-restorable teeth, caries, periapical pathology, edentulism and denture stability [11].

An additional benefit of early dental consultation when a BTA is being considered, is that the patient is educated about the long term risk to the oral cavity associated with these therapies and directed back to BC Cancer Oral Oncology/Dentistry if they should ever require dental extractions in the future to prevent the development of MRONJ.

The American Association of Oral and Maxillofacial Surgeons (AAOMS) Position Paper on MRONJ may be found at:

https://www.aaoms.org/docs/govt_affairs/advocacy_white_papers/mronj_position_paper.pdf

SPECIAL CONSIDERATIONS IN SPECIFIC CANCERS

V. PROSTATE CANCER

Q1. What is the approach to the optimization of bone health in patients with castration sensitive prostate cancer?

- Antiresorptive therapy is recommended in men on ADT for >6 months with either a BMD T score of <-2.0 or those with 2 or more risk factors for fracture. (ESMO guidelines section 3).

- Alendronate, risedronate, pamidronate and zoledronate have all been shown to prevent bone loss from ADT in patients with locally advanced prostate cancer. Of these treatments, zoledronate (4-5 mg) given every 6 to 12-monthly and denosumab (60 mg) every 6 months are considered the most convenient and reliable treatments. However, only denosumab has regulatory approval for treatment-induced bone loss associated with ADT.

Q2. What is the approach to the optimization of bone health in patients with castration resistant prostate cancer?

- Patients with castration-resistant prostate cancer with bony metastasis should be offered bone targeted agents with zoledronic acid 4 mg every 1-3 months or denosumab 120 mg every month for prevention of SREs.

Q3. What are the safety considerations in patients receiving bone-targeted therapy in metastatic castration resistant prostate cancer?

- Optimal safe duration of monthly therapy for prevention of SREs is not well established. Pivotal trials treated patients for a maximum of 24 months. Incidence of ONJ as well as the risk for atypical femoral fractures may increase with longer duration of exposure. As noted previously, patients should be counselled on either continuing denosumab or transitioning to another antiresorptive agent in order to prevent rapid bone loss that occurs after discontinuation of denosumab [6].

- Monthly blood work is recommended before denosumab 120 mg monthly injections or zoledronate 4 mg monthly infusions [12].

- Hypocalcemia should be corrected before injection or infusion. Renal function should be assessed before zoledronic acid is administered as the use of this medication is restricted to patients with an eGFR >35. Hypocalcemia is more common in patients with renal insufficiency after potent antiresorptive therapy.

VI. BREAST CANCER

Q1. Among patients with breast cancer receiving endocrine therapies, how do you identify patients that would benefit from anti resorptive therapy?

The ESMO guidelines (section 3) recommend that women with a bone density T score of -2.0 or less should receive preventive antiresorptive therapy if on aromatase inhibitor. Those patients with additional risk factors and T score -1.5 are also candidates for treatment.

Q2. Which metastatic breast cancer patient should be considered for bone targeted therapy?

Breast cancer patients with bony metastatic disease may benefit from bone targeted therapy. Initiating therapy at an early stage of bone metastatic disease may be more effective at preventing later skeletal -related events.

VII. GYNECOLOGIC CANCERS

Q1. When is menopause early?

- The average age of natural menopause is 52 in North America.
- Premature Menopause is defined as menopause occurring at or before age 40 [13]. This can occur naturally or be induced.
- Early menopause is defined as menopause between ages 40-45.
- Premature menopause is associated with an increased risk of osteoporosis [14], incident cardiovascular disease [15] as well as symptoms such as flushes, night sweats, vaginal dryness, and cognitive decline [16].

Q2. How should we manage early menopause due to cancer therapy?

- Hypogonadism or premature menopause (age < 45 yr)" is a major risk factor for osteoporosis and a baseline BMD should be ordered based on Osteoporosis Canada 2010 Guidelines (https://osteoporosis.ca/clinical-practice-guidelines/)
- For healthy women with premature and early menopause, hormone replacement is recommended until the average age of menopause approximately age 50-52 unless contraindicated.
- Hormone replacement typically involves taking estrogen, and for women who still have a uterus, a progestogen or equivalent is also recommended to protect the uterus from unwanted effects from estrogen [17].
- Hormone replacement therapy in this population reduces bone loss [18] and improves quality of life [19].
- For women with a history of premature menopause due to cancer, the recommendations for hormone replacement vary based on the type of cancer. For many cancers, such as cervical, the benefits outweigh the risks [20].

Q3. How should we manage breast cancer "Previvors" with surgical menopause?

- A previvor is someone who has an elevated predisposition to being diagnosed with cancer due to a familial or genetic cause[21]. This section refers to women who do not have cancer but have been treated proactively due to their high risk. This population is distinct and different from patients who

have had breast cancer, where hormone replacement is contraindicated due to the results of the HABITS trial [22].

- After risk reducing bilateral salpingo-oopherectomy (RRBSO) with or without mastectomy, hormone replacement does not increase oncologic risk and should be considered for women with early menopause and generally should be continued at least until the normal age of menopause[23].
- Studies have shown inconsistent use of hormone replacement and bone health surveillance in these patients, despite their increased risk of osteoporosis [24] including a population-based study done in British Columbia [25].
- The North American Menopause Society recommends that young previvors with or without intact breasts should not delay or avoid risk-reducing BSO because of concerns that subsequent use of systemic hormone replacement will elevate breast cancer risk [21].
- The British Columbia Cancer Agency (BCCA) offers support for these patients: http://www.bccancer.bc.ca/coping-and-support-site/Documents/Hereditary%20Cancer%20Program/HCP_GuidelinesManuals_HBOC.pdf

VIII. RADIATION INDUCED OSTEOPOROSIS

Q1. How does radiation treatment affect bone health?

- Specific bone complications of radiation include loss of bone mass, growth arrest, fracture and malignancy. Loss of bone mass is typically reversible and severity is dose dependent. Insufficiency fractures generally affect those bones under most physiologic stress and with the highest ratio of trabecular to cortical bone [26]. Osteoporosis risk factors are closely associated with the development of insufficiency fractures [27].

Q2. What are the rates of insufficiency fractures in genitourinary and gynecologic cancers treated with radiation?

- Reported cumulative incidences of insufficiency fractures after pelvic radiotherapy range between 8.2 to 45.2% in cervical cancer, 9% to 11.2% in rectal cancer, and 6.8% in prostate cancer [28].

BIBLIOGRAPHY

1. Manolagas, S.C., et al., *The role of estrogen and androgen receptors in bone health and disease.* Nat Rev Endocrinol, 2013. **9**(12): p. 699-712.
2. Hadji, P., *Aromatase inhibitor-associated bone loss in breast cancer patients is distinct from postmenopausal osteoporosis.* Crit Rev Oncol Hematol, 2009. **69**(1): p. 73-82.
3. Morote, J., et al., *Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer.* Urology, 2007. **69**(3): p. 500-4.
4. Coleman, R., et al., *Bone health in cancer: ESMO Clinical Practice Guidelines.* Ann Oncol, 2020. **31**(12): p. 1650-1663.
5. Shapiro, C.L., et al., *Management of Osteoporosis in Survivors of Adult Cancers With Nonmetastatic Disease: ASCO Clinical Practice Guideline.* J Clin Oncol, 2019. **37**(31): p. 2916-2946.
6. Symonds, C. and G. Kline, *Warning of an increased risk of vertebral fracture after stopping denosumab.* CMAJ, 2018. **190**(16): p. E485-E486.
7. Himelstein, A.L., et al., *Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial.* JAMA, 2017. **317**(1): p. 48-58.
8. Henry, D., et al., *Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors.* Support Care Cancer, 2014. **22**(3): p. 679-87.
9. Hallmer F, et al., *Prevalence, initiating factor, and treatment outcome of medication-related osteonecrosis of the jaw-a 4-year prospective study.* Oral Surg Oral Med Oral Pathol Oral Radiol, 2018. **126**:477.
10. Aljohani S, et al., *What is the effect of antiresorptive drugs (ARDs) on the development of medication-related osteonecrosis of the jaw (MRONJ) in osteoporosis patients: A systematic review.* J Craniomaxillofac Surg, 2017. **45**:1493.
11. Hinchy NV, et al., *Osteonecrosis of the jaw - prevention and treatment strategies for oral health professionals.* Oral Oncol, 2013. **49**:878.
12. Nasser, S.M., et al., *Effect of denosumab versus zoledronic acid on calcium levels in cancer patients with bone metastasis: A retrospective cohort study.* J Oncol Pharm Pract, 2019. **25**(8): p. 1846-1852.
13. Christin-Maitre, S., et al., *Position statement on the diagnosis and management of premature/primary ovarian insufficiency (except Turner Syndrome).* Ann Endocrinol (Paris), 2021. **82**(6): p. 555-571.
14. Anagnostis, P., et al., *Association between age at menopause and fracture risk: a systematic review and meta-analysis.* Endocrine, 2019. **63**(2): p. 213-224.
15. Honigberg, M.C., et al., *Association of Premature Natural and Surgical Menopause With Incident Cardiovascular Disease.* JAMA, 2019. **322**(24): p. 2411-2421.
16. Ryan, J., et al., *Impact of a premature menopause on cognitive function in later life.* BJOG, 2014. **121**(13): p. 1729-39.
17. Armeni, E., et al., *Hormone therapy regimens for managing the menopause and premature ovarian insufficiency.* Best Pract Res Clin Endocrinol Metab, 2021. **35**(6): p. 101561.
18. Costa, G.P.O., et al., *Impact of hormone therapy on the bone density of women with premature ovarian insufficiency: A systematic review.* Maturitas, 2023. **167**: p. 105-112.
19. Ishizuka, B., *Current Understanding of the Etiology, Symptomatology, and Treatment Options in Premature Ovarian Insufficiency (POI).* Front Endocrinol (Lausanne), 2021. **12**: p. 626924.
20. Deli, T., et al., *Hormone Replacement Therapy in Cancer Survivors - Review of the Literature.* Pathol Oncol Res, 2020. **26**(1): p. 63-78.
21. Domchek, S. and A.M. Kaunitz, *Use of systemic hormone therapy in BRCA mutation carriers.* Menopause, 2016. **23**(9): p. 1026-7.
22. Holmberg, L., et al., *HABITS (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped.* Lancet, 2004. **363**(9407): p. 453-5.

23. Gordhandas, S., et al., *Hormone replacement therapy after risk reducing salpingo-oophorectomy in patients with BRCA1 or BRCA2 mutations; a systematic review of risks and benefits.* Gynecol Oncol, 2019. **153**(1): p. 192-200.
24. Chapman, J.S., et al., *Surveillance of survivors: follow-up after risk-reducing salpingo-oophorectomy in BRCA 1/2 mutation carriers.* Gynecol Oncol, 2011. **122**(2): p. 339-43.
25. do Valle, H.A., et al., *Bone health after RRBSO among BRCA1/2 mutation carriers: a population-based study.* J Gynecol Oncol, 2022. **33**(4): p. e51.
26. Pacheco, R. and H. Stock, *Effects of radiation on bone.* Curr Osteoporos Rep, 2013. **11**(4): p. 299-304.
27. Ikushima H, et al., *Pelvic bone complications following radiation therapy of gynecologic malignancies: clinical evaluation of radiation-induced pelvic insufficiency fractures.* Gynecol Oncol, 2006. **103**: p. 1100–04.
28. Oh, D. and S.J. Huh, *Insufficiency fracture after radiation therapy.* Radiat Oncol J, 2014. **32**(4): p. 213-20.