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Aromatase Inhibitor-Induced Bone Loss And Its Management In Postmenopausal Women With Breast Cancer

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Abstract: Estrogen plays an important role in the development and growth of hormone-dependent breast cancer. Third generation aromatase inhibitors (AIs) have been established as the gold standard for treatment of hormone-dependent breast malignancy in postmenopausal women. AIs act by blocking the conversion of androgens to estrogens via aromatization. Since estrogen is the principal regulator of bone formation and AIs have an estrogen antagonistic effect. AIs can decrease bone mineral density (BMD) and thereby increase the risk of osteoporosis and fractures. Main goal of management of AI-induced bone loss (AIBL) is to minimize fracture risk, manage fracture associated symptoms, improve bone mass and increase performance status of patients. Patients at risk of BMD loss should be identified and managed based on clinical guidelines. All patients initiated on AI therapy should be assessed for fracture risk by BMD measurement using dual energy X-ray absorptiometry at baseline and annually in conjunction with fracture risk assessment tool. All patients should be educated about the risk of bone loss and annual monitoring of BMD before the initiation of AI therapy. Based on the fracture risk and T-score of individual patients supportive therapy with calcium and vitamin D supplements ± bisphosphonates or denosumab should be started concurrently for prevention of AIBL & subsequent risk of fracture. Even patients with normal T-score at baseline should be prescribed supportive therapy with calcium and vitamin D supplements concurrently with AIs and should be advised on need for physical activity and regular exercise for improving bone health.

Index Terms **-** Aromatase inhibitors, bone mineral density, breast malignancy, postmenopausal women, T-score

I. INTRODUCTION

Breast cancer is the most commonly diagnosed malignancy worldwide. [1] GLOBOCAN [2, 3] data reported an estimated 1.7 million new cases of breast neoplasm in 2012. The incidence of breast cancer in India is comparatively lower than that of the western countries. As per Indian council of medical research population based data, the incidence of breast cancer in India is 1, 44,000 annually with a wide variation in distribution ranging from 5 per 100,000 female population per year in rural areas to about 30 per 100,000 female population in urban areas. Therefore it has now become the most frequent female cancer in urban India. [4] Increasing numbers of postmenopausal women (PMW) are diagnosed with breast malignancy. [1]

Breast neoplasm is the fifth most frequent cause of death among women but decrease in mortality is seen in recent years. [1, 3] Early diagnosis and improved therapeutic regimens have significantly increased the survival in breast malignancy. Longer survival has, however, lead to recognition of long term adverse effects secondary to breast cancer therapy especially bone loss and fractures in patients treated with hormonal agents. [5]

Most of the patients with breast cancer are treated with chemotherapy, anti-human epidermal growth factor receptor (HER2/neu) therapy, endocrine treatment or a combination of these depending on the biomarker of the tumor. [6] Approximately 60% of breast malignancy expresses estrogen receptors (ER) suggesting estrogenic stimulation for tumor growth and progression. [7] The aim of hormonal treatment in breast cancer is to negate this stimulatory effect. [8] Breast malignancy which occurs in women older than 50 years are generally estrogen positive [9] and therefore can be treated by blocking ER, or by modulating (down regulating) the ER or by reducing the production of estrogen hormone from non-ovarian sources. [10]

II. PHYSIOLOGICAL ROLE OF ESTROGEN IN BREAST CANCER

Estrogen plays an important role in the development and growth of hormone-dependent breast cancer. [11] The connection between estrogen and breast cancer growth and development was recognized more than a century ago. [12] The concept that estrogen plays a critical role in the development and progression of breast cancer first emerged in 1896 with the observation by George Beatson that elimination of ovarian function by oophorectomy could benefit women with breast cancer. [13] Estrogen has effect on target tissues by binding to ER and therefore stimulates normal breast epithelium and malignant cell proliferation. [11] Various risk factors for breast neoplasm including early menarche, late menopause and postmenopausal obesity reflect increased cumulative lifetime exposure to estrogen. [14]

In premenopausal women ovaries are the primary source of estrogen but in PMW when ovaries are no longer functional, estrogens are produced mainly in the adipose tissues and adrenals by the conversion of androgens to estrogens via aromatization. In PMW breast has been recognized as an important site of estrogen production. Estrogenic stimulation of breast neoplasm and other target sites around the body is mediated through ER. [15]

It is estimated that 60-70% of breast neoplasm are ER positive and the proportion increases with increase in age. The most important predictor of response to hormonal treatment is the ER status of the tumor [11, 16]. Estrogens can significantly induce progesterone receptors as well (Figure 1). Testing the tumor for both estrogen and progesterone receptors is a standard part of breast neoplasm assessment. Currently the most frequent method used to test a tumor for estrogen and progesterone receptors is called immunohistochemistry (IHC). IHC testing can detect estrogen and progesterone receptors in formalin fixed paraffin embedded samples. [17, 18]

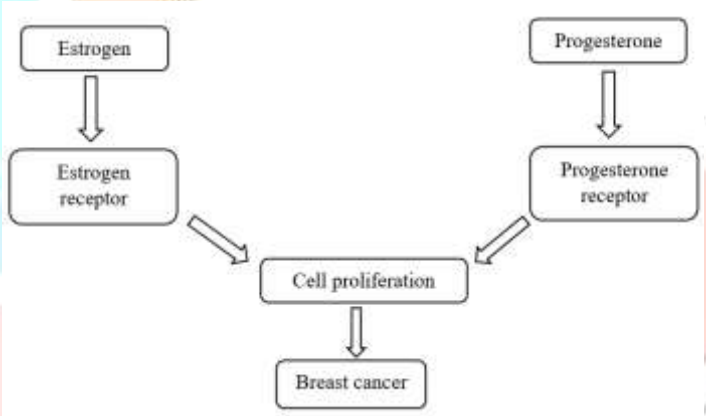

Figure 1: Role of estrogens and progesterones in development of breast cancer.

III. PHYSIOLOGICAL EFFECT OF ESTROGEN ON BONE

Estrogen is an important regulator of bone formation. Estrogens directly regulate bone metabolism through ER on osteoblasts, osteoclasts and osteocytes and indirectly through cytokines such as insulin like growth factor-1, interleukin-1 and 6, leptin neuropeptide-Y, transforming growth factor-β and tumor necrosis factor. [19, 20] Estrogens also regulate physiologic bone remodeling by suppressing osteoclast mediated bone resorption [21] (Figure 2). Breast malignancy itself affects bone metabolism by stimulating the release of transforming growth factor thereby increasing osteoclast activity. [1, 22]

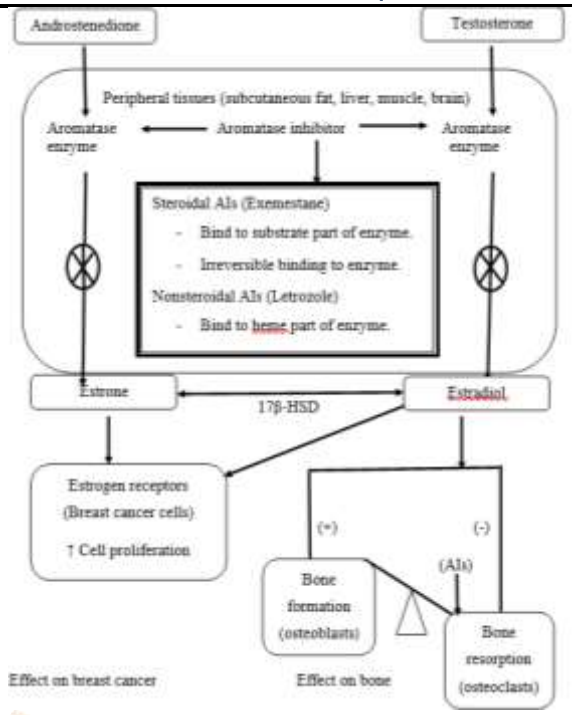

Figure 2: Mode of action of aromatase inhibitors and pathogenesis of aromatase inhibitor-induced bone loss. AIs: Aromatase inhibitors, **17β-HSD:** 17-β-hydroxysteroid dehydrogenase.

IV. MECHANISM OF ACTION OF AIs

The growth stimulatory effect of estrogen in breast neoplasm can be controlled either by disrupting the ability of estrogen to bind to its receptor or by reducing the circulating level of estrogen. Antiestrogens compete for binding to the ER and decrease the number of receptors available for estrogen binding. [10] Estrogen depletion can prevent or decrease estrogen dependent breast cancer which can be achieved through surgical or targeted hormonal therapy. [23] This has led to development of targeted antiestrogen therapy with tamoxifen or AIs. [10] AIs act by blocking aromatase enzyme (cytochrome P450 enzyme complex) which is involved in the rate limiting step responsible for conversion of androstendione to estrone (E1) and testosterone to estradiol (E2) in the peripheral tissues of PMW thereby decreasing the concentration of estrogen in breast (Figure 2). E1 can get converted to E2 and vice versa by sulfatase pathway with the help of 17β-hydroxysteroid dehydrogenase enzyme (17β-HSD). E1 is reduced by 17β-HSD to E2 and oxidative 17β-HSD catalyzes the conversion of E2 to E1. [24] Aromatase is produced in several tissues like adipose tissue, bones, brain, breast, liver, muscles, ovaries and skin. [25, 26] Activity of aromatase enzyme is elevated with age, alcohol intake, insulin, gonadotropins and obesity. [27]

In premenopausal women almost 95% of estrogen production takes place in the ovaries. [7, 27] Hence AIs are not effective in premenopausal women due to their inability to block ovarian production of estrogen. Due to the maximum synthesis of estrogen in adipose tissues, AIs are used for hormone-dependent breast cancer in PMW but not in premenopausal women. [28-30] But selected premenopausal women can also be treated with AIs after oophorectomy. [13]

There are three different therapy approaches with AIs for breast neoplasm and they include monotherapy as first line agent (5 years therapy with an AI), sequential adjuvant treatment (tamoxifen for 2-3 years followed by an AI for 2-3 years) and extended adjuvant therapy (tamoxifen for 5 years followed by AI for 5 years). AI treatment both as monotherapy and sequential adjuvant treatment have improved disease free survival in breast cancer patients.[31, 32] MA.17.R trial [33] suggests significantly lower incidence of contralateral breast cancer and higher rates of disease free survival with extended 10 years use of AI therapy compared to placebo. Various clinical trials [34, 35] have demonstrated the superiority of AIs over other ER activity suppressants in preventing disease recurrence, prolonging disease free survival and overall survival. Hence AIs have been established as the drug of choice in postmenopausal breast cancer patients. [6, 25]

V. AIs IN BREAST CANCER THERAPY

AIs are broadly classified into three generations based on the level of estrogen suppression (Table 1). First generation AIs inhibit the action of cytochrome P450 enzyme and reduces 91% of estrogens. [7, 36] Aminoglutethimide, an adrenal corticosteroid suppressant, was the first AI to be introduced. Toxicity and lack of selectivity of aminoglutethimide led to the development of novel AIs. [37] The steroidal inhibitors of 2nd and 3rd generations act by binding to the substrate binding site of aromatase enzyme, leading to the formation

of covalent bonds causing irreversible inactivation of the enzyme. On the other hand non-steroidal AIs bind non-covalently to the heme part of aromatase enzyme and prevent the interaction of androgen with the enzyme leading to reversible inactivation of aromatase. [36]

Second generation AIs reduce 85% of estrogens whereas third generation reduces approximately 97- 99% of estrogens, hence currently third generation AIs are the most preferred first line treatment of PMW with hormone-dependent breast cancer. Anastrozole, exemestane and letrozole reduces approximately 97%, 98% and 99% of estrogen. Though letrozole is the most widely prescribed AI, efficacy and safety profiles do not significantly vary between various members of the third generation AIs. [7] The lack of estrogen agonist activity of AIs is the reason for decreased risk of thromboembolism and uterine cancer as compared to tamoxifen. [37, 38]

Table 1: Classification of Aromatase inhibitors.

Types	Irreversible steroidal inhibitors	Reversible non-steroidal inhibitors
1st generation	-	Aminoglutethimide (250 mg tablet)
2nd generation	Formestane	Fadrozole
3rd generation	Exemestane (25 mg tablet)	Anastrozole (1 mg tablet) Letrozole (2.5 mg tablet)

VI. AROMATASE INHIBITOR INDUCED BONE LOSS (AIBL)

Both breast neoplasm and its treatment have an effect on bone metabolism. [39] Women with breast neoplasm are at greater risk of bone pain, reduced performance status and fractures due to estrogen induced bone loss. [40-42] All PMW are generally osteoporotic and susceptible to fracture. [43] Estrogen has a regulatory effect on bone turnover. [30] AIs have estrogen antagonist effect [5] which causes reduction in bone mineral density (BMD). During AI-associated estrogen depletion, osteoclast mediated bone resorption & osteoblast mediated bone formation are imbalanced (Figure 2), leading to bone loss [21] and increased risk of osteoporosis and fracture rate. [44] The incidence of fracture is higher with AIs compared to tamoxifen. [45] Common sites of minimal trauma fracture are hip, pelvis, wrist, forearm and spine. These fractures may affect body movements and functioning, which can result in disability, affect quality of life and lead to loss of independence. [46] In addition to morbidity, fractures are associated with high healthcare costs and increased healthcare utilization for several months after fracture incidence. [47] All AIs (steroidal and non-steroidal) almost have similar effects on bone. [48]

A cross-sectional study [49] has demonstrated that breast cancer women have low BMD with increased risk of fracture compared to women of the same age who did not have any cancer history. A Spanish study [50] of PMW with breast cancer reported that 17.7% patients had normal BMD while 60.1 and 22.2% patients had osteopenia and osteoporosis respectively before initiating AI treatment. BMD reduction in women treated with AIs was reported to be up to 17.3% in 3 years where as in healthy PMW an annual BMD reduction of 3% was shown. [22] Several studies [46, 51, 52] have reported that loss of bone mass and fractures in PMW receiving long term AIs are >30% or twice that of normal PMW of the same age. Hence women receiving AIs are at high risk for bone loss and fracture compared to healthy age matched women. [1, 38, 53]

VII. MEASUREMENT OF BMD

The gold standard for assessing osteoporosis and osteopenia is to measure BMD by dual energy x-ray absorptiometry (DEXA), which measures the bone density in two dimensions [52], is available since 1987. Safety, ease of use, short scanning times, low radiation exposure [54] are advantages of DEXA. WHO has established DEXA as the best bone densitometry technique for assessing BMD in PMW and has based the definitions of osteopenia and osteoporosis on T-score results derived from BMD. DEXA allows the diagnosis of osteoporosis, estimation of fracture risk by monitoring the BMD of patients undergoing treatment. DEXA machine is available in two types, hologic discovery and lunar prodigy. [55] Lunar prodigy (Figure 3) produces BMD data which is approximately 15% higher than that of hologic devices because the two types of scanners are calibrated in a different way. Although there is variation in calibration, when the BMD values are

transformed into T-scores there is barely any difference between the two machines provided that T-scores are calculated using the respective lunar or hologic devices. [56]

Osteoporosis and osteopenia are assessed on the basis of a BMD scaled by the T-score. [37, 57] BMD refers to the ratio of weight of the skeleton to the area of the bones measured .Thus the unit of BMD is g/cm^2. Difference between patient's BMD and that of a healthy young adult is measured in units called standard deviations (SDs). T-score is defined as difference between a patient's measured BMD and the mean BMD of young gender-matched normal population, divided by the SD of the BMD of the young normal population. [53] According to WHO criteria for PMW a T-score of ≥ -1 SD is considered 'normal' and a T-score of -1 to -2.5 SD as 'osteopenia' while a T-score of ≤ -2.5 SD is considered osteoporosis. [37]

Z-score is calculated by comparing a patient's BMD to that of an age-matched group. Z-score is defined as difference between a patient's measured BMD and the mean BMD of the age-matched group divided by the SD of the BMD of the age-matched group. [53] An Z-score ≤ -2 is considered below the expected range for age and an Z-score > -2 as within the expected range for age. T-score and Z-score values are generated by the DEXA machine. [37] For every SD below peak BMD, fracture risk increases [58] by 50% to 100%.

Spine has biggest bone surface which is comprised of cancellous bone. Hence changes in bone turnover occur at spine first and this is the preferred location for measuring BMD. [59-61] DEXA of the lumbar spine (LS), hip, dual femur, and forearm are other sites of BMD measurement. There is evidence to suggest that the optimum site for predicting the risk of hip fracture is the femur and for monitoring the response to treatment is spine. [58, 62]

Figure 3: Lunar prodigy dual energy X-ray absorptiometry (DEXA) system by GE healthcare for BMD measurement.

VIII. FRACTURE RISK ASSESSMENT TOOL (FRAX)

FRAX was developed by the WHO collaborating center at Sheffield UK for metabolic bone diseases and was first released in 2008. [63, 64] FRAX tool is specific for different countries of the world. It is easy to use online tool for monitoring percentage risk of fracture in PMW. [64] FRAX is based on data from large scale population based cohorts from different parts of the world and uses various clinical risk factors like age, gender, body mass index (BMI) and risk factors comprising prior fragility fracture, parental history of fracture, current tobacco smoking, high alcohol consumption, long term oral glucocorticoid use, presence of rheumatoid arthritis and other causes of osteoporosis. [35, 65] FRAX tool, specific for India, is available as online software. [64]

The output of FRAX predicts the probability of a major osteoporotic fracture (femur, forearm, neck, humerus, spine, vertebral or wrist) [Low <10%, moderate 10-20% and high risk > 20%] and hip fracture (Low < 3% and high risk ≥ 3%) in the next 10years.[50, 64] Various validated risk factors of fracture in PMW with breast neoplasm include age >60 years, family history of hip fracture, low BMI (<20 kg/m^2), oral corticosteroids use >6 months, previous history of fracture after age 50, smoking and a T-score < -1.5 SD whereas chemotherapy, radiotherapy and low weight are possible risk factors.[66, 67]

At baseline, fracture risk assessment using both WHO FRAX and BMD is better than BMD alone. [63] A retrospective case controlled study in 402 postmenopausal breast cancer patients has shown that use of BMD alone resulted in <10% of the patients eligible for antiresorptive therapy whereas when BMD was combined with risk factors >28% of candidates were eligible for antiresoptive therapy. [68] Therefore there has been a greater awareness of the increased bone loss and fracture risk reported with the use of AIs [69, 70] with an increasing effort for proper management and interventions to reduce bone loss and prevent fragility fracture. [71-73]

IX. MANAGEMENT OF AIBL

Main goal of management of AIBL is to minimize fracture risk, manage fracture associated symptoms and improve bone mass, increase performance status, overall health and well-being of patients. [1] Various clinical trials indicate that the deleterious effects of AIs on skeleton can be managed with bisphosphonates and led to the development of clinical guidelines for prevention of AIBL. Recently several clinical guidelines [30, 67] have

been issued all of which recommend that women with breast neoplasm receiving AIs should have their bone health monitored. According to American society of clinical oncology guidelines [67] BMD is the primary indicator to direct treatment option for AIBL in breast cancer patients. [33] DEXA scan is recommended to assess BMD at the start of therapy and annually in patients receiving AIs. Additional risk factors should be evaluated concurrently with BMD measurements to determine fracture risk. [37]

It is necessary to initiate supportive therapy for bone loss early during AI therapy to minimize the effect on BMD loss and maintain patient's physical functioning. [37] BMD loss can be prevented by concurrent use of AIs with calcium and vitamin D supplements ± antiresorptive agents (Table 2). An algorithm for management of AIBL is shown in Figure 4. BMD can be preserved in patients treated with AI using bisphosphonates which are inhibitors of osteoclast mediated bone resorption. [38] Bisphosphonates/denosumab treatment is recommended in osteoporotic as well as in osteopenic patients with 1-2 risk factors of fracture. [1] Fracture risk increases by 7.7-11% with AI therapy but can be reduced by initiation of bisphosphonates along with the AIs. [74] Randomized clinical trials (Table 3) have shown that oral and intravenous bisphosphonates and denosumab may be beneficial for the management of AIBL and useful in increasing BMD and thereby preventing fractures.

Table 2: Antiresorptive agents for prevention of AIBL

Drug	Route of administration	Strength and Dosage form	Frequency of administration	Annual cost (₹)
Alendronate	Oral	70 mg tablet	Once weekly	1450
Denosumab	Subcutaneously in the upper arm, thigh or abdomen	60 mg prefilled syringe	Once every 6 months	28,780
Ibandronate	Oral	150 mg tablet	Once monthly	5540
	Intravenous over 15-30 seconds	3 mg prefilled syringe	Once every 3 months	5520
Risedronate	Oral	35 and 50 mg tablets	35 mg once weekly or 50 mg monthly	3120
Zoledronic acid	Intravenous infusion over > 15 minutes	4 mg/100 ml vial	Once every 6 months	5980

AIBL: Aromatase inhibitor-induced bone loss.

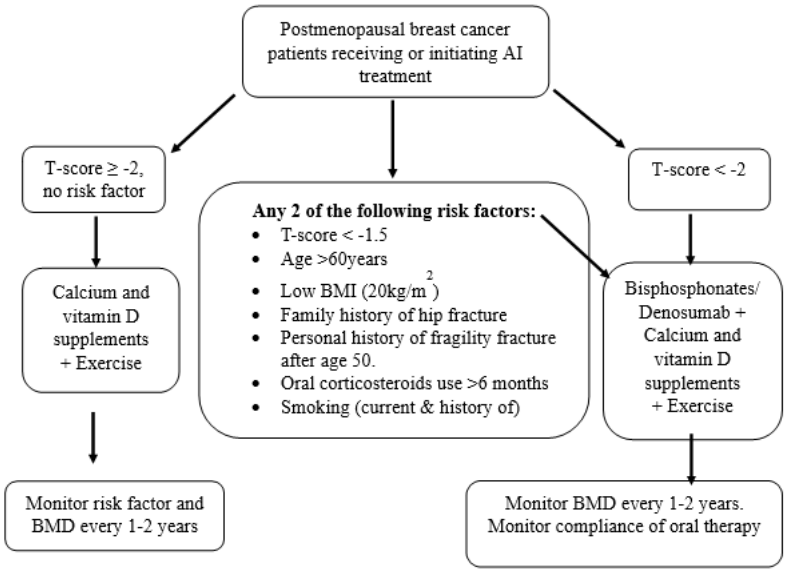

Figure 4: Algorithm for management of AIBL in women with breast cancer initiated on AI therapy [5, 67]

Zomata®-Femara® trials [52, 82] (Z-FAST and ZO-FAST) were designed to observe whether intravenous zoledronic acid 4 mg given every 6 months at initiation of AI therapy will provide benefit over zoledronic acid given at the first sign of bone loss. After 5 years of follow-up, Z-FAST study indicated that zoledronic acid with initiation of AI therapy increased LS (6.2%) and total hip BMD (2.6%) whereas delaying zoledronic acid (if T-score < -2 or fracture) led to loss of BMD -2.4% at LS and -4.1% at total hip. [52] Similarly in ZO-FAST study has shown increase in BMD at LS by 4.4% and by 1.9% at total hip for women receiving zoledronic acid with AI at 3 years of follow-up. The PMW who received delayed zoledronic acid had a decrease in BMD by -4.9% at LS and -3.5% at total hip. [82] Likewise after 3 years of follow-up similar results of BMD improvement and losses were shown in E-ZO-FAST study. [83] After a follow-up of 3 years, ZO-FAST study showed higher disease free survival with a 41% risk reduction of disease recurrence in patients who were initiated concurrently letrozole and zoledronic acid compared to the delayed group. [82] Administration of Zoledronic acid on the initiation of AI therapy decreases the release of the biochemical markers of bone turnover and thereby prevents bone loss and additionally it decreases disease recurrence. [52, 82] Zoledronic acid seems to be effective in the management of AIBL as well as estrogen-dependent breast cancer. Antineoplastic effect of bisphosphonates in a meta-analysis conducted by the early clinical trial group has shown reduction in the incidence of bone resorption by 34% and breast cancer mortality by 17%. But bisphosphonates do not have regulatory approval for the prevention of breast cancer recurrence which limits prescribing ability unless patient meets the AIBL criteria. Intravenous Zoledronic acid is considered to have better efficacy compared to oral bisphosphonates for prevention of AIBL. [46]

Regular measurement of BMD and adherence to supplemental therapies such as intake of calcium and vitamin D supplements and non-pharmacological therapies such as fall prevention, lifestyle changes and physical activity should be encouraged. [67] Vitamin D deficiency is more frequent in the general population including PMW. [86, 87] When PMW receive calcium and vitamin D supplements, bone turnover reduces due to closing of the gaps of remodeling. [5] For PMW receiving AI treatment, concurrent use of vitamin D at a daily dose of 800-2000 IU and calcium 1200 mg is recommended to maintain replete level. Meta-analysis [88] has suggested that intake of vitamin D or calcium supplements alone are not effective for the prevention of fracture risk in breast malignancy patients. Consumption of calcium for long term was shown to reduce the risk of osteoporosis up to 20%. This was confirmed in another meta-analysis [89] where postmenopausal elderly men and women showed a reduction of fracture risk by 18%. Majority of patients received calcium and vitamin D supplements which increases BMD by 1% and reduces fracture. Vitamin D supplements also have positive effects in the prevention of cardiovascular diseases, hypertension, falls, cancer incidence and mortality. [90,91]

All patients should be educated about the risk of bone loss before the initiation of AI therapy. Assessing both BMD and risk factors can help to identify elevated risk of fracture in breast neoplasm patients and to select the suitable preventive treatment. [86] Due to elevated fracture risk early prevention is recommended in breast neoplasm patients. Patients treated with AI should be educated about assessment of BMD by DEXA scan at baseline and annually for identification of increased risk of bone loss. [92] Additional risk factors of fracture should also be taken into account to make therapeutic decisions for patients at moderate risk of fracture. [93]

Based on FRAX tool patients who are identified as high risk of major osteoporotic fracture or hip fracture or those with a history of previous fracture should be initiated pharmacologic treatment along with AI therapy. [94] Even patients with normal T-score at baseline should be advised to take supportive therapy with calcium D supplements concurrently with AIs. Based on current data intravenous infusion of zoledronic acid 4mg at 6 months interval is most preferred therapy for the prevention of AIBL. Alternate antiresorptive agents can be considered based on individual patients. Denosumab 60 mg subcutaneous injection at intervals of 6 months is also considered a therapeutic option for the management of AIBL but not used commonly due to its high cost. [85]

X. CONCLUSION

Reduction in bone mineral density (BMD) is an inevitable consequence of AI therapy. Hence patients who are intended to receive AI therapy should be educated about risk factors of fractures as well as assessing BMD at baseline and annually and about the initiation of supportive therapies such as calcium and vitamin D supplements ± bisphosphonates/denosumab for the prevention of AIBL. In all patients initiating AI therapy, fracture risk should be assessed with BMD measurement as well as by FRAX tool and based on the risk of fracture of individual patients, supportive therapy should be started concurrently with the AI to prevent BMD loss and subsequent risk of fracture.

XI. Acknowledgment

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