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Recommendations and metaanalyses

French recommendations on strategies for preventing and treating osteoporosis induced by adjuvant breast cancer therapies

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ABSTRACT

Standard adjuvant therapies for breast cancer such as chemotherapy or aromatase inhibitor and LH-RH agonist hormone therapy are associated with significant survival gains but also induce bone loss by aggravating the estrogen deprivation. The bone loss may be substantial, notably during early treatment, and occurs regardless of the baseline bone mineral density values. The objective of developing these recommendations was to achieve a practical consensus among various scientific societies, based on literature review, about osteoporosis prevention and treatment in these patients. The following scientific societies contributed to the work: Société Française de Rhumatologie (SFR), Groupe de Recherche et d'Information sur les Ostéoporoses (GRIO), Groupe Européen d'Etudes des Métastases Osseuses (GEMO), Association Francophone pour les Soins Oncologiques de Support (AFSOS), Société Française de Sénologie et de Pathologie Mammaire (SFSPM), Société Française de Radiothérapie Oncologique (SFRO). Drug prescription and reimbursement modalities in France were taken into account. These recommendations apply to postmenopausal women taking systemic chemotherapy and/or aromatase inhibitor therapy, non-postmenopausal women taking LH-RH agonist therapy, and non-postmenopausal women with persistent amenorrhea 1 year after chemotherapy completion. All women in these three categories should undergo an evaluation of bone health and receive interventions to combat risk factors for bone loss. Patients with a history of severe osteoporotic fracture and/or a T-score value <-2.5 should receive osteoporosis drug therapy. The FRAX® score should be used to guide treatment decisions in patients whose T-score is between −1 and −2.5. General osteoporosis prevention measures should be applied in patients without criteria for osteoporosis drug therapy, who should undergo bone mineral density measurements 18–24 months later if the baseline T-score is < −1 and 3–5 years later if the baseline T-score is > −1. The anti-tumor effect of bisphosphonates and denosumab was not considered when establishing these recommendations.

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1. Introduction

Breast cancer is the most common malignancy in women, with an estimated number of new cases in 2017 of 58,968 in continental France, compared to 20,837 for colorectal cancer and 16,849 for lung cancer. Breast cancer accounts for 31.2% of all incident cancer cases in women. Breast cancer was the largest contributor to the estimated 66,000 deaths from cancer in women in continental France in 2017, with 11 883 patients, followed by lung cancer (10,176 patients) and colorectal cancer (8390 patients). In 2012, median age at diagnosis was 63 years and median age at death was 73 years [1].

In addition to local surgical and/or radiation therapy, patients with nonmetastatic breast cancer may be given adjuvant systemic therapies, whose modalities are determined during a multidisciplinary discussion. These adjuvant therapies include chemotherapeutic agents, anti-HER2 monoclonal antibodies, and hormone treatments such as tamoxifen, aromatase inhibitors, and/or LH-RH agonists [2]. Tamoxifen is the most widely used adjuvant hormone therapy in women with breast cancer diagnosed before the menopause. Ovarian suppression by an LH-RH agonist combined with tamoxifen or an aromatase inhibitor is a less common strategy. In women diagnosed after the menopause, hormone therapy usually consists in one of the third-generation aromatase inhibitors (anastrozole, letrozole, or exemestane), which have been proven to decrease the risk of recurrence and were more effective than tamoxifen in most studies [3]. Among adverse effects, the risk of endometrial cancer is higher with tamoxifen, whereas the risk of fractures is higher with aromatase inhibitors [4].

By hastening the menopause or further decreasing estrogen production in postmenopausal women, chemotherapeutic agents, LH-RH agonists, and aromatase inhibitors can decrease bone mineral density (BMD) values and increase the fracture risk.

2. Methods

These recommendations are intended for all physicians who manage patients requiring osteoporosis prevention and treatment due to the use of adjuvant chemotherapy and/or hormone therapy for breast cancer. They apply to postmenopausal and non-postmenopausal women who receive not only local surgical and/or radiation therapy but also systemic treatment with chemotherapeutic agents and/or hormonal agents (tamoxifen, aromatase inhibitors, LH-RH agonists). The management of bone metastases is not considered in these recommendations.

The objectives of these recommendations are to improve patient management; to limit the risk of fractures due to bone loss induced by adjuvant breast cancer therapies, while taking into account the efficacy and safety of these treatments, as well as their indications and current reimbursement modalities in France; and to suggest treatment strategies appropriate for each clinical situation.

The content of these recommendations was established in compliance with the method advocated by the French High Authority for Health (*Haute Autorité Sanitaire*, HAS). The recommendations were drafted by two project managers and a panel of scientific experts then discussed and revised by a multidisciplinary panel of reviewers. When the published data on which to base a recommendation were inadequate or incomplete, a professional consensus taking current practices and expert opinion into account was developed during a process that included a review of the latest European and American recommendations [5–9]. Taking every specific situation including each comorbidity and each hospital management protocol into account would not have been feasible, and the recommendations reported here cannot therefore reflect the full spectrum of possible management approaches. Thus, these recommendations cannot be viewed as relieving physicians from their individual responsibilities to their patients.

The following six scientific societies participated in the development of these recommendations: Association Francophone pour les Soins Oncologiques de Support (AFSOS), Groupe Européen d'Etudes des Métastases Osseuses (GEMO), Groupe de Recherche et d'Information sur les Ostéoporoses (GRIO), Société Française de Radiothérapie Oncologique (SFRO), Société Française de Rhumatologie (SFR), Société Française de Sénologie et de Pathologie Mammaire (SFSPM). Each of these societies designated representatives, who contributed to elaborate the recommendations by participating in the task forces and review panels.

3. Bone effects of adjuvant breast cancer therapies

The incidence of breast cancer in most studies was higher in postmenopausal women with high bone mass values indicating greater estrogen exposure [10–15] and lower in women with a history of osteoporotic fractures [16,17]. The adjuvant chemotherapies and hormone therapies used in breast cancer aggravate the estrogen deprivation, thereby causing bone loss and increasing the risk of osteoporotic fractures [18,19]. The prevalence of osteoporotic fractures early in the course of aromatase inhibitor therapy ranges from 10% to 20% [20–22]. Whether breast cancer per se exerts effects on bone tissue is unknown.

3.1. Effects of chemotherapy on bone

The chemotherapeutic agents used to treat bone cancer in non-postmenopausal women induce the menopause or temporary amenorrhea in 25% to 90% of cases [23–28], with variations according to age and chemotherapy protocols. Thus, permanent ovarian failure is more common among women older than 40 years, and loss of menses correlates significantly with age [25,29]. The development of amenorrhea is significantly correlated with a decline in BMD values [29]. In women who remain amenorrhoeic after 1 year, reported BMD declines are about 6% at the lumbar spine and 5% at the proximal femur [29–33].

No BMD or fracture risk data are available for assessing specific effects of chemotherapy or concomitant glucocorticoid therapy in postmenopausal women.

3.2. Effects of hormone therapy on bone

3.2.1. Bone effects of aromatase inhibitors (anastrozole, letrozole, exemestane)

The effects on BMD values have been investigated for aromatase inhibitor therapy used after chemotherapy [34–41], sequentially after 2–3 years of tamoxifen [42,43], in extension studies after 5 years of tamoxifen [44], and for prevention [45,46]. BMD values were usually measured 12 to 24 months after aromatase inhibitor initiation. During primary aromatase inhibitor therapy, BMD declines after 12 and 24 months at the lumbar spine were 2.2% and 3.9%, respectively, with anastrozole in the ATAC study and 2.6% and 3.5%, respectively, with exemestane in the TEAM study. These decreases were significantly greater than in the tamoxifen group. Corresponding BMD losses at the total hip were 1.5% and 3.9%, respectively, with anastrozole in the ATAC study and 1.3% and 3.3%, respectively, with exemestane in the TEAM study; again, the decreases were significantly greater than those seen with tamoxifen. Five-year data are available only for the ATAC study and show BMD decreases of 6% at the lumbar spine and 7.2% at the total hip [34].

BMD values at the lumbar spine decrease more rapidly during the first 2 years after aromatase inhibitor therapy initiation than during the next 3 years. At the total hip, in contrast, the pace of

the BMD decline does not slow over time. Among women whose baseline T-score was > −1, none had a T-score < −2.5 after 5 years of aromatase inhibitor therapy. After treatment discontinuation, the BMD lost during treatment may be partially regained [47–49]. In the ATAC study, lumbar spine BMD values increased by 2.35% and 4.02%, respectively, 1 and 2 years after treatment discontinuation, whereas BMD values at the total hip remained stable.

Nonsteroidal aromatase inhibitors (anastrozole and letrozole) may have different effects on bone from those of the steroid aromatase inhibitor exemestane, whose metabolite 17-hydroexemestane exerts androgenic effects that may explain the lesser bone loss seen in animals [50]. However, the only available study comparing exemestane to anastrozole in women found no difference in the BMD declines after 2 years [40].

The levels of markers for bone resorption and formation increase during aromatase inhibitor therapy [35,41,44,51], with no significant differences across drugs [40,52,53].

The fracture risk was higher in women given aromatase inhibitors than tamoxifen in virtually all the available studies [36,42,54,55]. None of the extension studies after 5 years of tamoxifen found a higher fracture risk with aromatase inhibitor therapy compared to a placebo [44,56,57].

The incidence of fractures varied widely from one study to the next, in part due to differences in the methods used to collect fracture events. After 36 months, the fracture incidence was 1% in the ITA study [58] and 9.6% in the ABCSG-18 study [59]. Importantly, the number of fractures was small and follow-up limited in most studies. In addition, the absence of routine spinal imaging may have resulted in some fractures being missed, and misclassification may have occurred between traumatic and nontraumatic fractures.

3.2.2. Bone effects of tamoxifen

The effects of tamoxifen on BMD values depend on the hormonal status at treatment initiation. In postmenopausal women, compared to a placebo, tamoxifen maintains BMD values at the lumbar spine and proximal femur [60–62]. In non-postmenopausal women, tamoxifen, although one of the selective estrogen receptor modulators (SERMs), exerts antagonistic effects on bone. The scant data available for this population indicate that tamoxifen fails to prevent bone loss compared to a placebo, inducing BMD declines of 1% to 2% per year at both measurement sites [60,63].

In two case-control studies, tamoxifen was not associated with fracture risk modifications [64,65].

3.2.3. Bone effects of LH-RH agonists

In non-postmenopausal women, LH-RH agonists consistently induce amenorrhea. Menses resume within 1 year in three-quarters of patients. In the Zoladex Early Breast Cancer Research Association (ZEBRA) and Zoladex in Premenopausal Patients (ZIPP) studies, 2-year BMD decreases at the lumbar spine ranged from 5% to 10%, and partial BMD recovery was noted after treatment discontinuation in those women whose menses resumed [33,66]. No data on the fracture risk during LH-RH agonist therapy are available.

4. Fracture risk evaluation in patients taking adjuvant chemotherapy and/or hormone therapy for breast cancer

A baseline fracture risk evaluation is recommended (professional consensus) in postmenopausal women starting aromatase inhibitor therapy, non-postmenopausal women with persistent amenorrhea 1 year after chemotherapy, and non-postmenopausal women taking an LH-RH agonist combined with tamoxifen or an aromatase inhibitor.

The identification of patients at risk for fractures rests on a multifactorial evaluation of the characteristics of each patient, history of low-energy fractures, risk factors for osteoporosis, risk factors for falls, BMD values, and cancer treatments.

Table 1
Clinical risk factors for fractures.

Age
Age at menopause < 40 years
Primary or secondary amenorrhea
Body mass index < 19 kg/m^2
History of osteoporotic fracture
History of proximal femoral fracture in a first-degree relative
Glucocorticoid therapy for longer than 3 months in a dosage > 7.5 mg/day
History of neuromuscular disease
History of prolonged immobilization
Impaired vision
Alcohol abuse
Smoking
Low calcium intake
Vitamin D deficiency

4.1. History of fractures

The main risk factor for further fractures is a history of low-energy fracture, whose identification is therefore a crucial component of the fracture risk evaluation (Grade A). Osteoporotic fractures can involve any site except the skull, face, cervical spine, first three thoracic vertebras, hands, and toes. They occur after a low-energy trauma such as a fall from standing height. The risk of death is increased in patients with major or severe osteoporotic fractures, which are defined as fractures of the hip, proximal humerus, spine, pelvis, distal femur, proximal tibia, and at least three ribs [67]. Osteoporotic fractures at other sites such as the forearm, which are classified as non-severe, are not associated with excess mortality.

Vertebral fractures may cause little or no symptoms. Height must be measured at each visit and compared to the height at 20 years of age. Spinal radiographs should be obtained only if the loss of height is ≥ 4 cm versus the height at age 20 or ≥ 2 cm during follow-up or if the patient reports back pain (professional consensus). Dual-energy X-ray absorptiometry machines can provide a vertebral fracture assessment (VFA), which is effective in screening for vertebral fractures but is not reimbursed by the French statutory healthcare insurance system.

4.2. Risk factor evaluation

4.2.1. Evaluation of risk factors for osteoporotic fractures

Risk factors for bone loss in addition to the use of adjuvant breast cancer therapy should be identified to improve the fracture risk evaluation (Table 1).

4.2.2. Evaluation of risk factors for falls

Risk factors for falls strongly influence the likelihood of fractures occurring in the oldest patients. Over 80% of nonvertebral fractures are caused by falls. In 2005, the French HAS issued the following recommendations about identifying patients at risk for falls (http//www.hassante.fr/portail/upload/docs/application/pdf/prevention_des_chutes-argumentaire.pdf): patients should be asked whether they have had one or several falls during the past year; if not, risk factors for falls should be sought or a few simple tests performed during the visit such as the get-up-and-go test, the single-leg stance test, and the sternal nudge test.

The G8 questionnaire (https://www.evidencio.com/models/show/1045) is a screening tool designed to determine when an in-depth geriatric evaluation is in order in patients with cancer who are older than 70 years. A score below 14 indicates a need for a geriatric evaluation.

4.3. Bone mineral density (BMD) measurement

BMD values should be measured in the following groups of patients (professional consensus): postmenopausal women starting aromatase inhibitor therapy, non-postmenopausal women with persistent amenorrhea 1 year after chemotherapy completion, and non-postmenopausal women on LH-RH agonist therapy combined with tamoxifen or an aromatase inhibitor. BMD measurement in these patients subgroups is reimbursed in France.

The measurement sites are the lumbar spine and the proximal femur (femoral neck and total hip). The results should be interpreted by using the T-score for all adult women (non-postmenopausal and postmenopausal). During the perimenopausal period, the T-score is comparable to the Z-score.

4.4. FRAX® score

The FRAX® score, whose use is recommended by the World Health Organization, estimates the absolute 10-year risk of hip fractures and major fractures in individuals older than 40 years (www.sheffield.ac.uk/FRAX) [68]. The risk factors used to compute the score were identified, and their predictive value assessed, by a mega-metaanalysis of 12 international cohorts. These risk factors are age, body mass index, history of fractures, history of proximal femoral fracture in a parent, current smoking, glucocorticoid therapy, rheumatoid arthritis, other causes of secondary osteoporosis, alcohol abuse, and BMD at the femoral neck.

The FRAX® score was validated in populations of healthy postmenopausal women but not specifically in women treated for breast cancer and may underestimate the fracture risk in this population. Adjuvant breast cancer therapy should be included among the causes of secondary osteoporosis when computing the FRAX® score (professional consensus).

Computing the FRAX® is unhelpful in patients who clearly meet criteria for osteoporosis therapy (professional consensus).

In France, the FRAX® score cutoff used to determine whether osteoporosis therapy is in order varies with age: at a given age, the FRAX® cutoff for the risk of major fracture indicating a need for osteoporosis therapy is the risk in same-age women with a history of fracture [69].

4.5. Bone turnover marker assays

No evidence exists that assays of markers for bone resorption and/or formation help to guide treatment decisions in women with bone loss induced by breast cancer treatments. Furthermore, the use of bone turnover marker values to predict the fracture risk is not recommended (Grade A).

5. Treatment prerequisites

5.1. General measures

The measures described below should be made available to all women targeted by these recommendations (professional consensus).

5.1.1. Eliminate modifiable risk factors

Modifiable risk factors for fractures and falls must be identified and eliminated. The measures may include the cessation of smoking and of alcohol abuse, correction of vitamin D deficiency, and dietary modifications to increase the calcium intake. Glucocorticoids should be prescribed in the minimum effective dosage.

5.1.2. Laboratory workup

A basic laboratory workup must be performed to rule out other causes of bone fragility and to identify any contraindications to osteoporosis treatment. The tests must include the following: blood cell counts and platelet count; erythrocyte sedimentation rate or C-reactive protein level; serum levels of calcium, phosphate, creatinine, and total alkaline phosphatase; serum protein electrophoresis; parathyroid hormone; and 25(OH)vitamin D (professional consensus).

5.1.3. Fall prevention

Fall prevention measures include prescribing physical activity programs, hazard-proofing the home, correcting visual impairments, and adjusting antihypertensive and/or hypnotic drug regimens. These measures are important in elderly patients.

5.2. Calcium intake

The French National Health and Nutrition Program (*Programme National Nutrition Santé*, PNNS) recommends a daily dietary calcium intake of 800 to 1200 mg, i.e., four helpings of dairy products (e.g., yogurt, cream cheese, fermented milk, cheese, and milk) per day. Self-administered food frequency questionnaire for assessing the dietary calcium intake is available online (e.g., www.grio.org). Routine calcium supplementation without an assessment of dietary intake is not recommended (Grade A).

5.3. Vitamin D intake

As inadequate vitamin D stores may exacerbate the adverse effects of adjuvant breast cancer therapies on bone, the serum 25(OH)D level optimal for bone health must be maintained. This optimal level has been defined as 30 ng/mL (75 nmol/L). However, the biological and clinical studies on which this definition is based did not focus specifically on osteoporosis induced by adjuvant breast cancer therapies. Importantly, several studies found decreased breast cancer recurrence rates in patients with 25(OH)D levels above 20 ng/mL (50 nmol/L) [70,71]. Consequently, a serum 25(OH)D assay should be obtained to allow adjustment of the loading vitamin D supplementation dose (Grade A).

Patients with vitamin D deficiency or insufficiency should receive a loading dose of vitamin D to increase the serum 25(OH)D level above the 30 ng/mL target (Grade A). Cholecalciferol in doses of 100,000 IU can be given at 2-week intervals as follows [72]: vitamin D deficiency (25(OH)D < 10 ng/mL), four doses; severe vitamin D insufficiency, (25(OH)D between 10 and 20 ng/mL), three doses; and mild vitamin D insufficiency, (25(OH)D between 20 and 30 ng/mL), two doses. Cholecalciferol doses of 80 000 IU can also be used.

The dose required for maintenance therapy is usually between 800 and 1200 IU/day (or the equivalent intermittent doses of 80,000 to 100,000 IU every 2–3 months) but should be tailored to each patient.

The use of lower vitamin D doses at shorter intervals was suggested very recently, particularly for patients with a history of falls. Thus, a weekly dose of 50,000 IU can be used, with a treatment duration of 8 or 4 weeks depending on whether the 25(OH)D level is < 20 ng/mL or between 20 and 30 ng/mL. The maintenance dosage is then 50 000 IU/month [73].

The currently available data do not support the use of high doses at long intervals (e.g., 500,000 or 600,000 IU once or twice a year (Grade A).

Dihydroxyvitamin D derivatives are not recommended, notably because they can increase the urinary excretion of calcium (Grade A).

A repeat 25(OH)D assay should be obtained once during follow-up to adjust the maintenance supplement dose, notably in overweight or obese patients (professional consensus) (Fig. 1).

6. Strategies for using osteoporosis medications

These recommendations pertain to the prevention and treatment of bone loss induced by chemotherapy, aromatase inhibitors, and LH-RH agonists. The treatment modalities are based on the existing licenses of osteoporosis medications available in France.

Antiresorptive therapies for bone loss prevention may add to the effectiveness of breast cancer treatment, as they have been reported to decrease the risk of bone metastases and to increase overall survival. Several studies of various bisphosphonate regimens support these oncological benefits. More specifically, a metaanalysis of individual data available for bisphosphonates indicates improvements in cancer outcomes, which were most noticeable in postmenopausal women [74]. The results of studies of denosumab have not yet been published. The panel of experts decided that a conclusion about the oncological effects of antiresorptive therapies in patients with breast cancer would be premature.

6.1. Selecting patients for osteoporosis therapy

The following criteria should be used to select patients for osteoporosis therapy due to their high risk of fracture (Fig. 1): history of low-energy severe fracture (Grade A); T-score between −1 and −2.5 with a FRAX® score above the value in same-age women with a history of fracture (professional consensus); or no history of severe fracture but T-score ≤ −2.5 at any site (lumbar spine, femoral neck, or total hip) (professional consensus). For the last criterion, a T-score cut-off above that used in postmenopausal women without breast cancer was chosen because of the additional fracture risk conferred by adjuvant breast cancer therapies and of the documented BMD decline of about one-half of a standard deviation after 5 years in the ATAC study.

6.2. Selecting the osteoporosis medication

Antiresorptive therapies (bisphosphonates and denosumab) have been proven effective in preventing bone loss in several trials. Most of the interventional studies were performed in postmenopausal women and used BMD criteria to assess efficacy. Thus, few data are available on fracture prevention, which is the primary treatment goal.

6.2.1. Preventive and therapeutic efficacy in women taking adjuvant hormone therapy or chemotherapy

6.2.1.1. Adjuvant hormone therapy. Several bisphosphonates given orally or intravenously, as well as denosumab, have been proven effective in preventing the bone loss induced by adjuvant aromatase inhibitor therapy in patients with breast cancer (Tables 2 and 3). A few studies in patients taking tamoxifen and LH-RH agonists are also available. Denosumab therapy decreased the fracture risk in patients taking aromatase inhibitors.

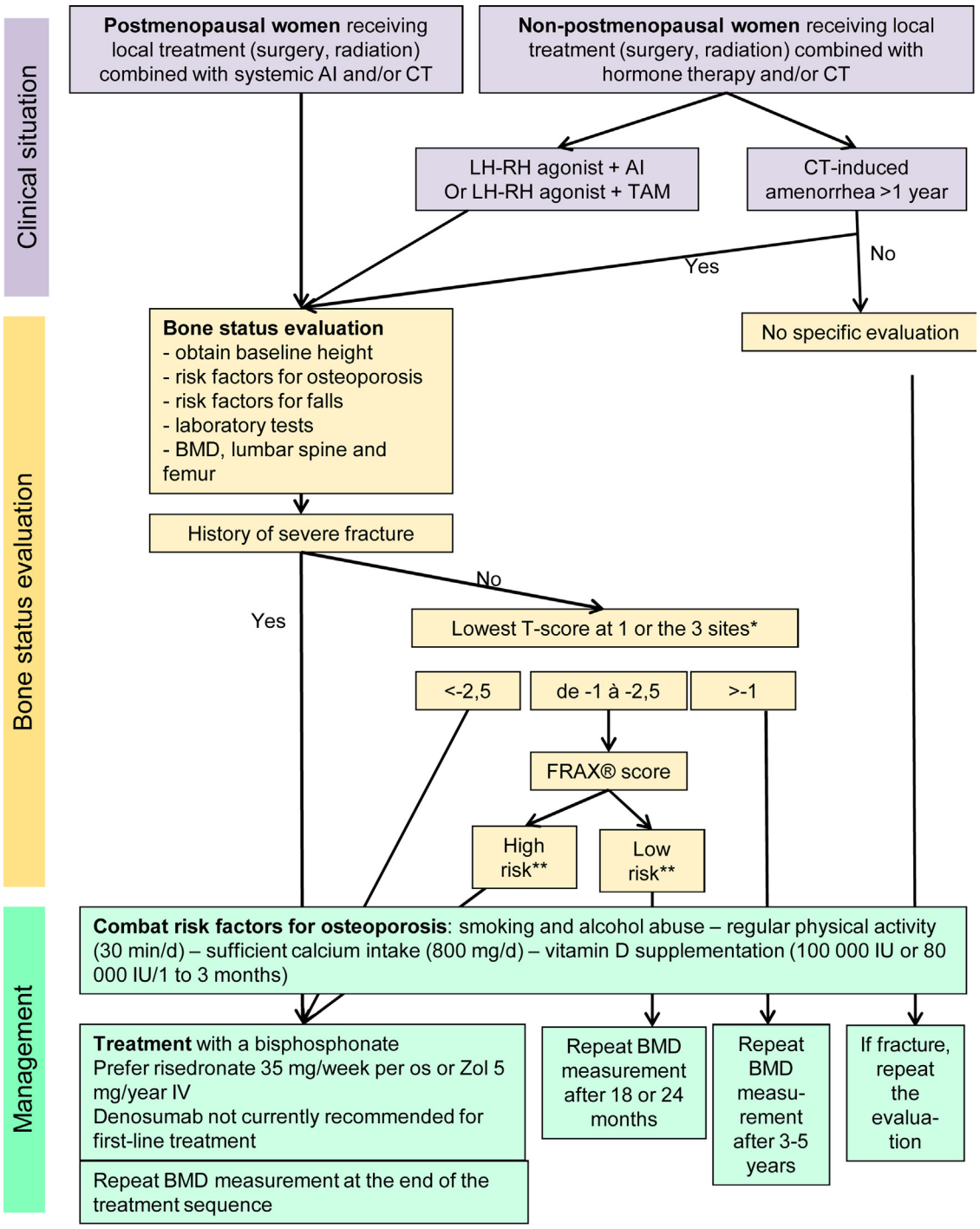
Among oral bisphosphonates, the most extensively studied is risedronate. In an open prospective cohort study of postmenopausal women on anastrazole therapy for breast cancer, bone loss was prevented at the hip and BMD increased significantly at the lumbar spine, by a mean of 4.1%, in the patients who had osteoporosis at baseline and were given risedronate 35 mg/week [75]. Patients scheduled to receive anastrazole were stratified on baseline T-score values in the IBIS II, SABRE, and ARBI studies [45,76,77]. Risedronate (35 mg/week) was given routinely in the group at high risk defined as a T-score < −2.5 in IBIS II and < −2.0 in SABRE and ARBI. Patients at moderate risk were randomized to risedronate or a placebo. The endpoint was BMD at the lumbar spine and hip after 2 years in SABRE and ARBI and after 3 years in IBIS II. Compared to the placebo, risedronate increased the BMD values at both sites. Similarly, a randomized placebo-controlled trial in 109 women with low bone mass treated with anastrozole, letrozole, or exemestane demonstrated beneficial effects of risedronate on bone mass after 2 years [78].

In the Australian BATMAN trial in patients taking anastrazole, alendronate (70 mg/week) was given to all 25 women with baseline osteoporosis and to 22 osteopenic women (T-score between −1 and −2.5) deemed eligible for osteoporosis therapy [79]. Of the 22 osteopenic women, 11 started alendronate within the first 18 months on anastrazole and 11 later on. After 3 years, the patients with baseline osteoporosis had significant BMD gains at the lumbar spine and femur. Significant BMD increases were noted at the lumbar spine only in the subgroup of osteoporotic women given early alendronate therapy. Caution is in order, however, given the very small sample sizes in this trial [79]. Another study, from South Korea, found a beneficial effect of alendronate therapy on lumbar spine BMD in patients taking aromatase inhibitor therapy but had a follow-up of only 24 weeks [80]. The 98 postmenopausal women included in this study took a combination of alendronate 5 mg and calcitriol 0.5 μg per os once daily or a placebo [80].

Ibandronate was evaluated in patients taking anastrazole in the ARIBON trial [81]. The patients with osteopenia (T-score between −1 and −2.5) were randomized to ibandronate 150 mg/month per os or a placebo. After 2 years, the ibandronate group had significant BMD gains versus baseline of 2.98% at the lumbar spine and 0.60% at the total hip, whereas BMD decreased by 3.22% and 3.90% at these two sites, respectively, in the placebo group ($P < 0.01$). In this trial, the 13 patients with osteoporosis at baseline were also given ibandronate and exhibited BMD increases after 2 and 5 years. However, ibandronate is no longer reimbursed in France for the management of osteoporosis.

Clodronate in a daily dosage of 1600 mg for 3 years was effective in preventing lumbar and femoral bone loss in postmenopausal women taking tamoxifen or toremifen [82]. Clodronate is not licensed for the prevention or treatment of osteoporosis.

Two different strategies were used in studies of zoledronic acid. The first, followed for instance in the ProBONE II trial [83,84], consisted in randomizing non-postmenopausal patients taking chemotherapy and/or hormone therapy to zoledronic acid (4 mg IV every 3 months) or a placebo. After 2 years (8 infusions), the treated group had BMD gains of 3.1% at the lumbar spine and 1.3% at the total hip, contrasting with decreases of 6.4% and 4.0% at these two sites, respectively, with the placebo ($P < 0.0001$). Moreover, zoledronic acid given only once every 6 months was effective in Korean postmenopausal women on aromatase inhibitor therapy [85] and in Austrian non-postmenopausal women taking the LH-RH agonist goserelin [86,87]. In the other approach used to investigate zoledronic acid in postmenopausal women, the drug was either started at the same time as the aromatase inhibitor letrozole (including in many patients with T-scores > −1) or was given only if and when a fracture occurred or the T-score fell below -2 during follow-up. This approach was used in the Z-FAST trial in North America; the ZO-FAST trial in Europe; the E-ZO-FAST trial that also included Latin American, African, and Asian countries; and the N03CC trial [88–96]. Follow-up in these studies was up to 5 years. The results were stratified based on whether adjuvant chemotherapy was given. Immediate zoledronic acid therapy consistently improved BMD values, even in recently postmenopausal women. In the N03CC trial, the patients were randomized to zoledronic acid or placebo only when they switched to letrozole after a period on tamoxifen alone [94,95]. After 5 years, despite considerable patient attrition, the placebo group had four times more patients with an at least 5% BMD decline at the lumbar spine (and



- Total lumbar spine, total hip, or femoral neck
- ** refer to the cutoff recommended for postmenopausal women

AI, aromatase inhibitor; CT, chemotherapy; Zol, zoledronic acid; BMD, bone mineral density; TAM, tamoxifen

Fig. 1. Recommendations for managing bone loss induced by adjuvant breast cancer therapies.

three times more with an at least 10% decline); at the femur, the difference in patient proportions was 6-fold (46% vs. 7.6%). Despite fairly long follow-ups, the fracture rates were not significantly different between groups in these studies, which were not however designed to assess this criterion.

The first randomized trial of denosumab (60 mg subcutaneously every 6 months) was performed versus a placebo in 252 postmenopausal women taking aromatase inhibitor therapy and having T-score values between −1 and −2.5, including 63% who had received chemotherapy [97,98]. Denosumab was effective in preventing induced bone loss after 1 year, with a 4.8% BMD increase at the lumbar spine compared to a 0.7% decrease in the placebo group ($P < 0.0001$); the BMD difference between the two groups was 5.5%. After 2 years, the BMD values in the denosumab group were higher than those in the placebo group by 7.6% at the lumbar spine, 4.7% at the total hip, 3.6% at the femoral neck, and

Table 2
Main studies of the effect of oral bisphosphonate therapy in women taking aromatase inhibitor therapy.

Treatments [reference] dosage	Number of patients (n) Study duration	BMD changes (%)					
		Lumbar spine			Total hip		
		Verum	Placebo	*P*-value	Verum	Placebo	*P*-value
Risedronate [75] 35 mg/week	*n* = 15 (open-label) 1 year	+4.1		0.008	+1.8		0.131
Risedronate [76] 35 mg/week PO	Intermediate BMD group (n = 114) High-risk group (*n* = 33) 2 years	+2.2 + 3.0	−1.8	<0.0001	+1.8 +2.0	−1.1	< 0.0001
Risedronate [77] 35 mg/week PO	Intermediate BMD group (*n* = 70) High-risk group (*n* = 93) 2 years	+5.7 + 6.6	−1.5	0.006	+1.6 −1.9	−3.9	0.037
Risedronate [45] 35 mg/week PO	Intermediate BMD group (*n* = 150) High-risk group (*n* = 46) 3 years	+ 1.1 + 1.2	−2.6	<0.0001	−0.7 +0.3	− 3.5	0.0001
Risedronate [78] 35 mg/week PO	*n* = 109 2 years	+2.3	−1.7	<0.0001	+0.6	−2.7	< 0.0001
Alendronate [79] 70 mg/week	Group with osteoporosis (*n* = 22) 3 years	+15.6			+ 5.6		
Ibandronate [81] 150 mg/month PO	Intermediate BMD group (*n* = 50) 2 years	+2.98	−3.2	<0.01	+ 0.6	−3.9	< 0.01
	Group with osteoporosis 2 years: *n* = 11 5 years: *n* = 9	+3.03 +9.65			+3.18 +2.72		

BMD: bone mineral density; PO: per os.

Table 3
Main studies of the effects on bone mineral density of injectable resorption inhibitors in women on aromatase inhibitor therapy.

Treatments [reference] Dosage	Number of patients (n) Study duration	BMD changes (%)					
		Lumbar spine Verum	Placebo or no tt	*P*-value	Total hip Verum	Placebo or no tt	*P*-value
Zoledronic acid [85] 4 mg IV/6 months	*n* = 107 3 years	+3.8	−8.2	< 0.0001	+1.8	−6.8	< 0.0001
Zoledronic acid [89] 4 mg IV/6 months	*n* = 602		−5.2			−6.13	
	Immediate tt	+6.2		< 0.0001	+2.6		< 0.0001
	Delayed tt 5 years *n* = 1065	−2.4			−4.1		
Zoledronic acid [91] 4 mg IV/6 months	Immediate tt	+4.3		< 0.0001	+1.6		< 0.0001
	Delayed tt 5 years n = 527	−5.4			−4.2		
Zoledronic acid [94] 4 mg IV/6 months	Immediate tt Delayed tt 1 year *n* = 199	+2.7 −2.7		< 0.0001	−1.72 −1.59		< 0.0001
Zoledronic acid 4 mg IV/6 months [93]	Immediate tt Delayed tt 1 year *n* = 558	+2.9 −2.0		< 0.001	+2.0 −2.4		< 0.001
Zoledronic acid [96] 4 mg IV/6 months	Immediate tt Delayed tt 2 years	+4.9 −2.2		< 0.001	+1.2 −3.3		< 0.001
Denosumab [97] 60 mg SC/6 months	*n* = 252 2 years	D = +7.6%		< 0.0001	D = +4.7%		< 0.0001
Denosumab [59] 60 mg SC/6 months	*n* = 3420 3 years	+7.3	−2.75	< 0.0001	+4.6	−3.3	< 0.0001

BMD: bone mineral density; tt: treatment; IV: intravenously; SC: subcutaneously; D: percentage difference between the verum and placebo groups.

6.1% at the distal radius ($P < 0.0001$). The BMD gains were not influenced by aromatase inhibitor treatment duration, type of aromatase inhibitor used, or previous history of tamoxifen exposure. In the ABCSG18 trial in 3420 patients on aromatase inhibitor therapy, denosumab decreased the risk of clinical fractures by 50% versus the placebo [59]. Denosumab significantly delayed the time to the first clinical fracture (hazard ratio, 0.50. 95%CI, 0.39–0.65; $P < 0.0001$) [59]. The estimated fracture incidence with denosumab versus the

Table 4
Effects of bisphosphonates on chemotherapy-induced bone loss in non-postmenopausal women.

Verum versus placebo	First author [reference]	Dosage	Duration (n)	Effects
Clodronate	Vehmanen [99]	1.5 g IV/course	7 courses (n = 45)	Lumbar spine bone loss: NS difference
	Powles [100]	1600 mg/d PO	At 2 years (n = 311)	Prevention of bone loss at the lumbar spine and femur
	Saarto [101]	1600 mg/d, PO 3 years	At 2 years (n = 148)	Decrease in lumbar spine and femoral bone loss (−2.2% vs. −5.9% at the lumbar spine, P = 0.0005; +0.9 vs. −2.0% at the total hip, P = 0.017)
	Velmanen [102]	1600 mg/d, PO 3 years	At 3 and 5 years (n = 73)	Decreased bone loss only at the lumbar spine (−3% vs. −7.4%; P = 0.003); bone loss remained less marked at the lumbar spine at 5 years, 2 years after clodronate discontinuation
	Saarto [103]	1600 mg/d, PO 3 years	At 10 years	Less induced osteoporosis after 10 years
Pamidronate	Fuleihan [104]	60 mg IV/3 months	1 year (n = 40)	Lumbar and femoral BMD gains if induced amenorrhea (+0.95% vs. −4.0% at the lumbar spine, P = 0.03; and +1.2 vs. −4.0% at the total hip, P = 0.003); NS in patients without amenorrhea
Risedronate	Hines [105]	35 mg/week PO	1 year (n = 216)	NS (−4.3% vs. −5.4% at the lumbar spine, P = 0.18; and −2.7% vs. −3.4% at the total hip, P = 0.40); high patient attrition rate of 21 %
	Delmas [106]	30 mg/d PO for 2 weeks, then 10 weeks without treatment (8 cycles of 12 weeks each)	2 years (n = 53)	Bone mass increased during treatment (differences were 2.5% at the lumbar spine, P = 0.041; and 2.6% at the femoral neck, P = 0.029). Bone loss during the year after discontinuation (year 3)
Zoledronic acid	Hershman [107]	4 mg IV/3 months	1 year (n = 101)	Prevention of bone loss (−0.6% vs. −4.4% at the lumbar spine −0.12% vs. −2.1% at the total hip P < 0.0001)
Studies of strategies				
Zoledronic acid	Shapiro [108]	4 mg IV/3 months (8 infusions)	2 years (n = 302)	Immediate treatment vs. treatment delayed for 1 year. After 1 year, prevention of bone loss (+1.4% vs. −5.5% at the lumbar spine, P < 0.001) even in women with induced amenorrhea (+1.2% vs. −6.7% at the lumbar spine, P < 0.001)
	Kim [109]	4 mg IV/6 months (8 infusions)	4 years (n = 112)	Immediate treatment vs. delayed treatment if and when a fracture occurred or the T-score fell < −2.5 Benefits from immediate treatment: −1.1% vs. −7.5% at the lumbar spine (P < 0.001); 1.1% vs. −3.4% at the total hip (P < 0.001)

IV: intravenously; PO: per os; NS: nonsignificant.

placebo was 5% vs. 9.6% at 36 months and 11% vs. 26.2% at 84 months. These results raise questions about the optimal duration and discontinuation modalities of denosumab treatment.

6.2.1.2. Adjuvant chemotherapy in non-postmenopausal women. No data are available on the use of denosumab to prevent chemotherapy-induced bone loss in non-postmenopausal women. Among bisphosphonates, clodronate [98–103], pamidronate [104], risedronate [105,106], and zoledronic acid given at chemotherapy initiation have been evaluated in placebo-controlled trials [107]. It should be noted that neither clodronate nor pamidronate are licensed for the prevention or treatment of osteoporosis (Table 4).

In two studies of treatment strategies, zoledronic acid was given routinely but was started either immediately or secondarily [108,109]. The study patients were young and were therefore often stratified on the history of tamoxifen exposure. BMD values were used to assess efficacy, with no data obtained on the incidence of fractures.

6.2.2. Recommendations

Risedronate, alendronate, or zoledronic acid may be used.

The recommended initial treatment is risedronate 35 mg per week. Alendronate may be used instead but has a smaller body of supporting data in women with breast cancer. Although published studies support the use of zoledronic acid 4 mg every 6 months, this regimen is neither licensed nor reimbursed in France. Consequently, the regimen of 5 mg intravenously once a year as used to treat postmenopausal osteoporosis is recommended (professional consensus).

Patients should be evaluated after 2–3 years and the results used to determine whether the treatment should be continued [69].

Published results obtained with denosumab suggest that 60 mg subcutaneously every 6 months may constitute an alternative in postmenopausal women. However, this treatment cannot be recommended as it is not licensed for use in this population and no long-term study has assessed outcomes after its discontinuation in this population (professional consensus). Denosumab should be considered only as a second-line drug. Reported evidence of rebound bone resorption after denosumab discontinuation

requires the administration of bisphosphonate therapy at the end of the denosumab sequence.

Given the absence of specific studies in this population and the need for caution regarding potential effects on tumor cells, no recommendation is made to use teriparatide, even in the absence of radiation therapy (professional consensus).

6.3. Obtaining specialist advice

Patients meeting any of the following criteria should be referred to a bone disease specialist: history of severe fracture, factors that make treatment decisions challenging (e.g., [T-score near −2,5, severe fracture and T-score > −1, history of non-severe fracture, or rapid bone loss early after treatment initiation]); and treatment failure.

7. Patient follow-up

7.1. Evaluating treatment adhesion

Treatments for osteoporosis, similar to all treatments for chronic diseases, are effective only if taken as prescribed. The drug used and administration modality should be discussed with the patient to optimize treatment adherence. Clinical follow-up may be sufficient to evaluate treatment adherence (professional consensus).

7.2. Role for bone mineral density (BMD) measurements during follow-up

BMD values should be measured at the end of the first osteoporosis treatment. In patients who are not given osteoporosis treatment, the bone loss induced by adjuvant breast cancer treatments requires periodic re-evaluations of the facture risk, with BMD measurements (professional consensus). The re-evaluation schedule should be determined based on the fracture risk profile of each patient and on the baseline BMD values (professional consensus) (Fig. 1).

7.3. Role for bone turnover marker assays during follow-up

In patients given osteoporosis treatment, an assay of a bone resorption marker such as serum CTX can be performed after the first 6 months to check that the value is within the normal range for non-postmenopausal women, reflecting the pharmacological effect of the drug. If the value is above normal, treatment adherence should be evaluated with the patient before considering a switch to a different drug. To obtain an interpretable result, the blood sample should be drawn in the morning after an overnight fast and at least 6 months after the last fracture if any (professional consensus). The level of evidence about the usefulness of bone turnover marker assays in improving treatment adherence is low.

7.4. Other follow-up procedures during treatment

Height should be measured at each visit or at least once a year. Vertebral fractures result in height loss. Height loss is a nonspecific indicator of spinal disease and may warrant spinal radiographs or a vertebral fracture assessment (professional consensus). A morphological assessment of the vertebras should be performed in patients with back pain or an at least 2-cm loss of height during follow-up.

7.5. Criteria for osteoporosis treatment discontinuation

Osteoporosis medication discontinuation can be considered at the end of the first treatment period in patients with no low-energy fractures while on the drug, no new risk factors, and no BMD decline $> 0.03\ g/cm^2$ at the lumbar spine or hip. However, in patients with a history of severe fracture, the treatment should not be discontinued unless the T-score at the end of the sequence is ≥ -2.5. In every case, the decision to stop osteoporosis therapy should rest on the risk/benefit evaluation in each individual patient (professional consensus).

7.6. Failure of osteoporosis treatment

When significant bone loss or a fracture occurs in a patient taking adjuvant breast cancer therapy and an osteoporosis medication, investigations for metastatic bone disease should be performed, treatment adherence should be assessed, and new risk factors for fracture should be sought. Ideally, advice should be obtained from a bone disease specialist.

8. Safety of osteoporosis medications

Bisphosphonate therapy to prevent or treat osteoporosis is associated with only low risks of osteonecrosis of the jaw (0.001% to 0.10%) and atypical femoral fractures. Nonetheless, patients should be informed about these adverse effects. The risk increases significantly with treatment duration and cumulative dose. Current data indicate that the benefits outweigh the risks. Patients should see their dentist regularly and practice good oral hygiene as recommended by the French Society for Stomatology, Maxillofacial Surgery, and Oral Surgery (*Société Française de Stomatologie, Chirurgie Maxillo-Faciale & Chirurgie Orale*, SFSCMFCO) [110]. Patients should also be informed about rare adverse effects such as uveitis.

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