Prevention and treatment of bone fragility in cancer patient

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Summary

It is well known that fractures increase the risk of morbidity and mortality. The various mechanisms responsible for bone loss in cancer patients may have a different impact depending on the characteristics of the clinical case and correlates with the therapies used, or caused by the therapies used against cancer. Some hormonal treatments cause hypogonadism, event which contributes to the progressive loss of bone mass. This is detectable in patients with breast cancer receiving determines that estrogen-deprivation and in men with prostate cancer with therapies that determine androgen deprivation. Chemotherapy treatments used in cancer patients have reduced bone mass. In addition, low bone mass is detectable in patients with lymphoma treated with corticosteroids or radiation or alkylating agents. In premenopausal patients suffering from breast cancer, treatment with cytotoxic therapy or ablation of ovarian function, can lead to an 8% reduction in bone mineral density at the spine and 4% in the femur. With a chemotherapy regimen in CMF, the reduction of BMD is 6.5%; this bone loss is not recovered after discontinuation of therapy. Tamoxifen given for five years reduces bone remodeling and cause a 32% increase in the risk of osteoporotic fractures when used in premenopausal. After menopause, tamoxifen has a protective effect on bone mass, with a reduced risk of new fractures. Aromatase inhibitors in post-menopausal women, depending on the formulation can cause different effects on the reduction of BMD and fracture risk. We have in fact steroids, exemestane and nonsteroidal, letrozole and anastrozole. Patients at increased risk of fragility fractures should undergo preventive therapies as soon as possible after tests performed for the study of bone health. They can be used DEXA and the FRAX algorithm, which can define a secondary osteoporosis. Prevention and treatment of the increased risk of osteoporotic fracture is to maintain adequate levels of calcium and vitamin D. Bisphosphonates and denosumab are used for the management of bone remodeling and bone loss induced by cancer treatments.

Bisphosphonates also have anti-tumor effects per se, which are expressed in potentially prevent the development of bone metastases. In men with metastatic prostate cancer and which is induced androgen deprivation, it is usefully used denosumab 120 mg monthly or zoledronic acid 4 mg monthly.

KEY WORDS: cancer; bone loss; bone resorption inhibitors.

Introduction

Osteoporosis is a common condition characterized by an impairment bone, of his strength and microarchitecture. These events increase the risk of spontaneous fracture (1). Cancer, after cardiovascular diseases, is still the second leading cause of death (30% of total mortality), however, it has a high survival rate at five years for at least some tumors (Table 1) (2). In testicular cancer, the endometrial cancer, melanoma, Hodgkin lymphoma and to a lesser extent in colorectal cancer, the survival prospects are similar to those of people who are affected by cancer. Incidence and prevalence of cancer are on the rise, partly because of an aging population. Mortality has instead a strong negative trend: in 2010 it is estimated that for breast cancer there are about 20 deaths per 100,000 women compared to nearly 40 deaths in 1990. Definitely have a role screening programs in health interventions secondary prevention; however, the identification of the attitude towards this ideal type of prevention is quite complex. The therapies used in oncology disease can cause considerable loss of bone mass and increase the risk of fragility fracture. Among these, aromatase inhibitors, chemotherapy, glucocorticoids and drugs that act on the pituitary gonadotropins, as their analogs, may contribute to an increase in bone remodeling leading to reduction of mineral density and an increase fracture risk. This also occurs in patients with prostate cancer treated with drugs that cause androgen deprivation. Breast cancer is one of the most common cancers among women, with more than one million cases and nearly 600,000 deaths each year around the world (3). The incidence of breast cancer is very different in various states. From the data of Italian cancer registries (AIRTUM) relative to 2013, it is estimated that there are in Italy during the year, 366,000 new diagnoses of cancer (excluding skin cancers), about 200,000 (55%) among men and about 166,000 (45%) among women. During the life of a man and a woman, 2 of 3 people will get sick of cancer. Considering the entire population, excluding skin cancers, the tumor by far the most frequent cancer of the colon (14%), followed by breast cancer (13%), prostate (11% in males only) and lung (11%). 70% of breast cancers are diagnosed in postmenopausal (4). The incidence of cancer is stable among men and women, the aging population is constantly increasing and at the same time increases the number of new cancer diagnosis. There are still differences in the frequency of cancer in our country with a lower incidence in the south, but that gradually is aligning with that of central and northern Italy.
indirect mechanisms, capable of slowing bone resorption.

Therefore, therapies for cancer induce hypogonadism may be tant to recognize the problem, assess the risks and identify those who could benefit from preventive therapy.

Estrogens are hormones that act on bone by direct and indirect effects of cancer treatments, both for inadequate intake calcium and vitamin D (9). Several chemotherapeutic agents may have direct effects on bone metabolism beyond hypogonadism. Systems employing high-dose chemotherapy, such as those used after hematopoietic stem cell transplantation (HSCT), exert their toxic dose dependent on osteoprogenitor cells. It is well known that radiation therapy can induce focal atrophy of the bone with the consequent increased risk of fracture (10). In fact, a study of postmenopausal women already before radical hysterectomy for cervical cancer or endometrial surgical treatment for these conditions has no causal role of osseous structures of the pelvis; this contributes to the development of pelvic fractures failure (11). Famously, a focal treatment with radiation at high doses can cause atrophy of the trabecular bone and subsequently treated with radiotherapy (RT), shows that surgical treatment for these conditions has no causal role of osteoporosis. While the RT after surgery involves an important role in bone loss. Histochesn studies previously conducted the bone of patients with cancer, have shown a higher activity osteoclastic and osteoblastic activity in addition to a reduction in bone mineral density (BMD) (8, 9). Radiation therapy used in advanced forms of cancer of the cervix and endometrium is conducted on the bony metastases. This contribution to the development of pelvic fractures failure (11). Famously, a focal treatment with radiation at high doses can cause atrophy of the trabecular bone and subsequently treated with radiotherapy (RT), shows that surgical treatment for these conditions has no causal role of osteoporosis.

Therapies for female cancers and the risk of fragility fractures

In patients with gynecologic cancers, particularly in patients with cervical cancer, it has been described a reduced bone mineral density of the spine (BMD) (5, 6). In addition, there are studies that examine the lifestyles and the risk of fracture in these patients. Women treated for cancer with surgery or chemotherapy have significantly reduced BMD vs subjects for benign disease or ovariectomized compared to healthy subjects of the same age (7). Estrogens are hormones that act on bone by direct and indirect mechanisms, capable of slowing bone resorption. Therefore, therapies for cancer induce hypogonadism may cause a condition of incresed bone fragility in a large percentage of patients (8). Treatments used in gynecological oncology are surgical castration, radiation therapy and chemotherapy, all determinants hypogonadism (8, 9). These therapies also have negative effects on bone metabolism, was directly that for indirect effects of cancer treatments, both for inadequate intake calcium and vitamin D (9). Several chemotherapeutic agents may have direct effects on bone metabolism beyond hypogonadism. Systems employing high-dose chemotherapy, such as those used after hematopoietic stem cell transplantation (HSCT), exert their toxic dose dependent on osteoprogenitor cells. It is well known that radiation therapy can induce focal atrophy of the bone with the consequent increased risk of fracture (10). In addition, glucocorticoids, cyclosporine, and L-thyroxine, drugs used in oncology, can cause a reduction in bone mineral density (BMD) (8, 9). Radiation therapy used in advanced forms of cancer of the cervix and endometrium is conducted on the bony metastases. This contribution to the development of pelvic fractures failure (11). Famously, a focal treatment with radiation at high doses can cause atrophy of the trabecular bone and subsequently treated with radiotherapy (RT), shows that surgical treatment for these conditions has no causal role of osteoporosis.

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BMD women with cervical cancer (17, 18). In particular, Nishio et al. (17) reported that patients with cervical cancer treated with concurrent chemotherapy and radiotherapy after surgery, showed a significant reduction in bone mineral density of the lumbar spine to 91.9 ± 5.9%. Hwang et al. (18) reported that the BMD of L4 and greater trochanter of the femur were significantly reduced compared to controls. On the other hand, adjuvant chemotherapy conducted in subjects with endometrial cancer in postmenopausal may not be related to cancer treatment-induced bone loss (17). The mineral depletion is faster and more severe in patients with treatment-induced bone loss in cancer compared to those natural menopause have a decrease in bone mass with the passage of years. Therefore, the prevention, detection and early treatment of cancer treatment-induced bone loss are essential to reduce the risk of fractures (8, 9) and also of other events related to the disease and its consequences such as depression, loss of self-esteem but they are also important for reducing health care expenditure, risks and identify those who could benefit from preventive therapy.

The treatment of breast cancer after surgery and osteoporosis

There are only small and isolated studies that evaluated bone health especially before the diagnosis of breast cancer (19, 20). The efficacy of ovariectomy (21) and adrenalectomy (22) used to induce estrogen deprivation, it is recognized as a critical block of tumor growth. Studies conducted in patients pre- and post-menopausal, have allowed us to demonstrate that estrogen derived from sources other than in relation to age of the patient. In over a century of basic research and clinical, endocrine therapy it provided a pharmacological armamentarium for the treatment of breast cancer. In 1998, Oxford has shown that the use of an estrogen receptor modulator drugs (SERMs), such as tamoxifen (TAM) used in breast cancer, in both pre and postmenopausal, it was equally as effective in the control of development of the tumor cells (23). TAM has become for many years the drug of choice for all cases of tumor with estrogen receptor positive (ER +). TAM, thanks to its estrogenic properties may reduce the risk of osteoporosis when used in post-menopausal women (24). However, the ovarian ablation conducted in premenopausal subjects can be associated with decreased bone mass up to 13% in the first year (25). Drugs that block the gonadotropin releasing hormone (GnRH), because similar to it, causing downregulation of the GnRH receptor and ovarian failure within 6 months of therapy (26), lead to a significant reduction in bone mineral density. This effect is higher than that in patients treated with adjuvant chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil-diagram CMF). In fact, in patients treated with goserelin, the BMD of the lumbar spine is reduced by 10.5%, compared with 6.5% of patients treated with CMF (p <0.001) (27). However, the cases treated according to the scheme CMF remain hypoestrogenic and so recover the bone loss after discontinuation of treatment. In contrast, patients treated with goserelin, have a recovery of bone density after only a year of stopping treatment, because these patients have the restoration of menstrual cycle (28).

Aromatase inhibitors (AI) - Mechanism of Action

Aromatase inhibitors (AI) are replacing TAM in the adjuvant hormonal therapy for women after menopause when cancer will be diagnosed early stage and with estrogen receptor (HR) positive. They act by inhibiting cytochrome P450 aromatase, an enzyme that catalyzes the conversion of androgens to estrogens. The first generation of these drugs (testolactone, aminoglutethimide) and second generation (formestane, fadrozole), are compounds characterized by less selective action and lower power compared to newer formulations and in use today: exemestane, anastrozole and letrozole (29). The current third generation IA inhibit 96-99% in vivo activity of the enzyme aromatase (30), thereby decreasing the levels of endogenous estrogens far below the levels from natural menopause (31). Inhibitors of type I drugs, steroidal compounds are derivatives of androstenedione, physiological substrate of aromatase. The non-steroidal AI, or Type II, are compounds derived from phe-nobarbital (such as aminoglutethimide) whose structure is characterized by the binding imidazole/triazole. The type of drug that binds covalently to the enzyme and leads to its irreversible inactivation. Conversely, the non-steroidal compounds are characterized by the reversibility of action. For postmenopausal women diagnosed with early-stage breast cancer and estrogen receptor (HR) positive, AI have been shown to have superior efficacy in reducing the risk of recurrence compared with TAM, and thus have become the preferred choice for this subgroup of patients. However, TAM remains a viable choice for initial hormonal therapy for those seeking to avoid the consequences for musculoskeletal effects of AI. This, as is clear from the results of a recent study (32), it is probably true for women at low risk of recurrence but who are at increased risk of fractures, as. In subjects with postmenopausal initial users TAM were slightly younger users of the AI, even though the former had significantly higher prevalence of history of osteoporosis. However, initial users TAM were more likely to have stage I disease than users initial AI, suggesting that even so their risk of recurrence was lower. Finally, a lower risk of relapse coupled increased risk of fracture may have influenced physicians and patients in favor of TAM IA as their first choice of initial hormonal therapy (32). The choice of doctors, based on the effectiveness of anticancer drugs IA third generation is not easy due to the lack of randomized controlled trials conducted in double blind have compared different preparations, postulating there are great differences in efficacy. Differences currently known power and differences in the structure and biochemical preparations third generation AI may result in differences in clinical efficacy. However, both the laboratory data that clinical data available suggest that they have a different toxicity profile. It should be noted that the toxicity profile is particularly relevant for older people who have a low cumulative risk of recurrence but a large number of co-morbidities, such as cardiovascular disease and osteoporosis. In a study on animal model, it is simulated the condition of breast cancer in postmenopausal women. In this study, tumor xenografts were obtained with the use of aromatase-overexpressing MCF-7 cells obtained from ovariecetomized mice. The Authors (33) have shown that tumors obtained with xenotransplantation, compared to ovariecotomized controls, have had a more rapid growth in size (diameter 8 mm) already 12 weeks after transplantation. However, in mice treated with anastrozole was recorded slower growth of the tumor in the active phase treatment, designed to replicate the treatment protocol of five years provided in women suffering from cancer, with an acceleration of growth upon cessation of drug AI. Moreover if they are also associated estradiol (100 pg / mL) and progesterone (6 ng / mL), was highlighted a significant reduction in body weight (about 16%), compared with that recorded by administering the
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only AI. A minimum of weight gain in animals, there was, similarly to mice during estrous, undergoing therapy with progesterone cyclical. Compared to control animals ovariectomized, the estrogen cyclical Association and AI determines final mass reduction of 31%, as was the case with the addition of testosterone. The study concludes that all the regimens used determine the final reduction of weight gain compared with controls and compared to ovariectomized rats treated with anastrozole alone. Therefore, since patients with oncological pathology deserve treatment decisions very balanced, according to the principle of primum non nocere, the desirable solution is to use the preparations are less toxic and more powerful among these medications (34).

Aromatase inhibitors and osteoporosis

The risk of osteoporotic women is closely related to the age of onset of menopause because estrogen deprivation is certainly the main factor in determining the loss of bone mass and increase the risk of fractures. The flavoring is notoriously the main way in which postmenopausal estrogen is still a reserve. In postmenopausal the body mass index is inversely proportional to the risk of osteoporosis. In this period, most of the androgens are converted into estrogen by the enzyme aromatase in the adipose tissue. All subjects treated with AI undergo a block of aromatization and this causes a decrease in BMD values. It follows that therapy with aromatase inhibitors increase the risk fracture, as is clear from the “Intergroup Exemestane Study” (IES) (35) and most of the studies. However, the reduction of bone mass is below using steroid AI, because of their androgenic activity that can have a stimulant effect on bone formation. Furthermore, the use of letrozole after a treatment with TAM used for five years it is, at least partially, to protect the bones from the deleterious effects of. In fact the study MA 17 (36) showed the differences in the rate of clinical fractures in spite of a significant change in bone mineral density in treated subjects AI, compared to those treated with placebo (31). The effects of different drugs on bone AI can be quantified with the rate of reduction of bone mass. In the study, the use of letrozole did not have the same effects (40, 41). In a randomized, placebo-controlled study in postmenopausal women show that early administration of exemestane versus placebo induced reduction in bone mineral density. This effect was only partially reversed in the course of a year of follow-up (39). In subjects randomized to exemestane arm of IES, markers of bone resorption have reached the highest levels after 12 months of treatment. Subsequently, it was observed reduction. Conversely, the markers of bone formation reach a peak between 18 and 24 months of treatment (42). Finally, the effects on serum and urinary biomarkers of bone turnover, after 24 months of treatment with exemestane, anastrozole or letrozole have also been described in a case series of 84 healthy postmenopausal women treated with letrozole and exemestane. Markers of bone resorption, the N telopeptide, it is increased to a greater extent with the use of letrozole, while the use of exemestane is associated with an increase propeptide in serum procollagen I N-terminal type 1 Plasma (P1NP), confirming the negative effects on bones training related to the androgenic nature of the drug (38).

Aromatase inhibitors and effects on plasma lipids, lipoproteins and cardiovascular system

The use of AI therapy is associated with a significant reduction in the risk of VTE, known to be high with the use of TAM. Other studies, the ATAC Trialists (37) and ARNO (43) also reported a significantly lower risk of cerebrovascular disease with the use of anastrozole. BIG 1-98 study showed that the use of letrozole could have a potential negative impact on the incidence of cardiovascular events. Although not significant, the overall difference was found in the incidence of heart failure and ischemic heart disease, with a significant excess of serious events (grade 3-5) of both types of the disease with the use of letrozole compared TAM (38). In addition, the potential negative effect of letrozole on the risk of cardiovascular disease can result from failure to show a protective effect of TAM rather than a true drug toxicity. However, this explanation is not entirely satisfactory because TAM used in chemoprevention has actually indifferent cardiovascular effects, both positive and negative (44), as is clear from a meta-analysis examining all adjuvant studies (45). The plasma levels of lipids and lipoproteins were measured to evaluate the effect of AI and hormone therapy on cardiovascular health in mice divided into two groups, the first of which treated with AI and the second group subjected to ovariectomy. After 5 and 10 months of treatment triglyceride levels decreased in the group treated with AI. The administration of estradiol (E) at different doses (40 pg / mL or 100 pg) and progesterone (P) (6 ng / mL) continuously or cyclically in the estrous phase, resulted in a significant increase in levels of triglycerides in the different groups hormone treatment compared to ovariectomized controls. AI therapy resulted in a significant increase in VLDL and LDL cholesterol. Adding E plus P together resulted significantly reduced levels of free cholesterol and VLDL / LDL compared to the group receiving only the AI. These effects are maintained even after 5, 10, and 15 months of combined therapy. The maximum reduction in levels of VLDL cholesterol / LDL was observed in the group treated simultaneously with E, P and testosterone (T). HDL cholesterol values showed significantly reduced in animals treated for 15 months with AI. This work suggests a higher average risk of cardiovascular disease (CVD) in these animals. Moreover, the association between AI, E and P shows the values of HDL those of mice subjected to ovariectomy. But the co-administration of E, P and T determines increase in HDL cholesterol, suggesting a possible cardiovascular risk reduction (33). In women, comparing all preparations AI against TAM, use of anastrozole (37) and letrozole (38) is associated with high cholesterol, as occurs with exemestane (35). A different effect of steroid preparations on drugs on the lipid profile was already noticed by Goss et al. (40, 41), which showed that 16 weeks of treatment with exemestane in ovariectomized rats prevented the significant increase in serum cholesterol and low density lipoprotein while this protective effect was not observed with letrozole. More recently, a comparison of the effects of exemestane compared with TAM on the lipid profile of patients with postmenopausal early breast cancer has been reported in preliminary results of the greek sub-study “team” (46) with a median follow-up of 12 months. The study found high levels of LDL in women treated with exemestane compared to the arm

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Prostate cancer and osteoporosis

Androgen receptor blocking agents have become an established form of therapy for men with prostate cancer spread. Androgen blockade, however, combined in older men with disseminated prostate cancer results in high bone turnover with a significant loss of bone (47). The androgens suppression therapy (AST) in patients with prostate cancer can dramatically affect the bone mineral density (BMD), which puts patients at risk of serious side effects such as bone fractures. The prevalence of osteoporosis in men with prostate cancer androgen deprivation therapy (ADT) is well documented, so that 53% of men with the disease suffers of osteoporosis. Also, there has been less emphasis on the weight of bone loss in men in the advanced stages of prostate cancer, but not subjected to ADT. A recent meta-analysis (48) shows the data for BMD of prostate hormone naïve patients, compared to subjects treated with ADT. In the works considered in the meta-analysis, the prevalence of osteoporosis. Low bone mass, and normal bone mass were estimated in these cases and comparison subgroups with similar from another meta-analysis of previously published. The prevalence of osteoporosis varies from 4-38% in patients with hormone-naïve prostate, with greater the prevalence of osteoporosis in patients with more advanced disease. In addition, people have a naïve hormone cases increased BMD in ADT. It remains high percentage of osteoporosis in patients with metastatic disease. This results suggest that all men with prostate cancer should have regular monitoring of bone health, regardless of the fact that the start ADT. The series of Chernichenko et al. (49) refers to date the comparison of subjects treated with hormone therapy intermittently flutamide at a dose of 250 mg three times day with nine monthly injections of lutetinizing gonadotrophic releasing hormone (LGnRH) (period of “treatment”). This step is followed by an observation period, during which no treatment is not administered. The evaluation of the lumbar spine and proximal femur by dual energy X-ray densitometry was performed either at the end of the period of “treatment” that the end of the period of “no treatment” (Table 2).

The prevention and treatment of osteoporosis in patients with cancer

Besides taking adequate calcium, vitamin D and implementation of regular physical activity, the options for prevention and treatment of osteoporosis in cancer patients include antiresorptive drug therapies. Ensure adequate vitamin D supplementation is a key component of the therapy in the prevention and treatment of osteoporosis. The effectiveness of calcium and vitamin D supplementation in the prevention of hip fracture was evaluated in Women’s Health Initiative trial, conducted on 36,282 postmenopausal women who received daily or 1000 mg of calcium and 400 IU of vitamin D or a placebo for about seven years (53). To take into account that these patients could take into autonomy even more supplements daily up to 1000 mg of calcium and 600 IU of vitamin D, but also bisphosphonates, calcitonin, SERM or estrogen. Compared to patients treated with placebo treated cases with 1000 mg of calcium and 400 IU of vitamin D daily, showed a 1.06% increase in BMD (p <0.01). In the group that carried out treatment in a manner consistent with the indications, the hazard ratio for hip fracture was 0.71 (95% CI, 52 to 0.97), which represents a statistically significant increase. It is observed 29% reduction in the risk of fractures in individuals taking more than 80% of their calcium and vitamin D. It was noted a small but significant increased risk of kidney stones in 17% of cases treated compared with placebo, with a relative risk of 1.17 (95% CI: 1.02 to 1.34) (53). The Advisory Board of the Osteoporosis Society of Scientific Canada (54) recommends:

- 1500 mg of elemental calcium per day and 800 IU of vitamin D per day for women and men 50 years of age;
- 400 IU of vitamin D per day and 1000 mg of calcium day for all adults under 50 years of age.

The antiresorptive therapies inhibit osteoclast activity and reduces bone turnover, each with different mechanisms of action. Estrogens act through the estrogen receptor on osteoblasts is that on osteoclasts, determine the suppression of the receptor activator factor kB ligand (RANKL) nuclear inhibition of osteoclasto differentiation and thereby reducing bone remodeling. Obviously in patients with oncological estrogen dependent, hormone replacement therapy is not indicated. Raloxifene (RAL), preparation of the selective estrogen receptor

Therapies for lymphoma, and myeloproliferative disorders the risk of fragility fractures

In patients with multiple myeloma who have rarefaction the trabecular meshwork due to infiltration plasma cells and osteoporosis deterioration of bone microstructure appears to be of value for assessing the risk of vertebral fracture and may indicate early stages of the processes osteolytic not yet visible (50). In adult patients treated for acute lymphoblastic leukemia (ALL) with total body irradiation - TBI were preliminarily evacuate both the late toxicity that the result of a series of 110 patients, of which 12 (11%) had symptoms of osteoporosis in long-term (51). The prevalence of low bone mineral density (BMD) in adult survivors all occurred in their childhood and the degree of recovery or decline, have been clarified recently by the study of subjects, aged ≥ 18 years and ≥10 years post-diagnosis. Aver-
modulator (SERM), it is able to bind to estrogen receptors, the effects with agonists or antagonists of tissue-specific bone, reducing remodeling, as well as also be equipped with extraskeletal effects. The class of drugs effects SERM shows tissue-specific agonist or antagonist to the estrogen receptor. Delmas et al. (55), it revealed that subjects treated for four years with RLA at the dose of 60 mg or 120 mg daily, it showed a 36% reduction, respectively, and 43% of the risk of vertebral fractures. It has not been shown, however, a significant effect on the risk of non-vertebral fractures probably for the average age of the subjects in therapy, in itself a low risk of hip fractures. Another comparison study done TAM and RAL administered in a cohort of 19,747 postmenopausal women at increased risk breast cancer. RAL was administered at a dose of 60 mg daily. The study pointed out the effects of the reduction in the risk of breast disease of cancer in equal measure with the administration of 20 mg per day of TAM for 5 years (56). Thus, it was demonstrated that both drugs reduce the risk of breast cancer by about 50%. In addition, TAM has been associated with a better safety profile than TAM, with 36% less of endometrial cancer and 29% less incidence deep vein thrombosis (56). Even anabolic therapy can lead to major improvements the quality and amount of bone, thus constituting an important option to antiresorptive therapies currently available. In subjects drugs in post-menopausal women with osteoporosis anabolic steroids agent teriparatide is the most powerful. In subjects drugs in post-menopausal women with osteoporosis anabolic steroids agent teriparatide is the most powerful that, however, can not be used in the prevention in cancer patients, at least during the first five years after diagnosis of solid tumor. Used for 18 months, can increase the production of bone matrix, improving osteoblast function and reducing the risk of fracture about 65% (57). Strontium ranelate has been shown to have antiresorptive property and also has anabolic properties (58, 59). But, strontium ranelate has been associated with an increased risk of thromboembolic events and should not be used in patients with VTE present or past or that are temporarily or permanently immobilized. More recently because concerns related to cardiovascular risk, the European Medicine Agency (2013) reported that the drug should also not be used in patients with inadequately controlled hypertension or by current or past ischemic heart disease, cerebrovascular disease or peripheral arterial disease. Take part in account of these security issues, according to the latest label strontium ranelate is indicated for the treatment of osteoporosis in grave men who have a high risk of fracture and can not be treated with other approved drugs for osteoporosis.

Bisphosphonates (BF)

Preparation of nitrogen (alendronate, risedronate, zoledronic acid) have antiresorptive effects and the sites of bone resorption bind hydroxypatite, where the bone matrix is exposed (60). The bisphosphonate is located in the context of recent formed bone that is inert and ineffective skeletal. During the step of bone resorption, the drug is released from the bone matrix and is ingested by osteoclasts. BF also inhibit farnesyl diphosphate synthase (FDPS), a key enzyme in the synthesis cholesterol. Inhibition FDPS affect multiple pathways involved in the organization of the cytoskeleton, acts on cell survival and proliferation, resulting in deactivation and apoptosis of osteoclasts (125). By means of these mechanisms the result is a reduced bone turnover and consequently, a higher mineralization skeleton. This leads to the normalization deli bone remodeling, improve the overall strength of the bone bringing its condition premenopausal parameters (61). Moreover, the contribution of BP during therapy for some tumors can become quote and synergy with other anticancer treatments having been proposed that they may be equipped with anti-tumor efficacy and also able to reduce the risk of bone metastases. Some observational studies also suggested a possible protective effect of bisphosphonates breast cancer (62). Analysing the case studies and FIT HORIZON-PFT, Hue et al. (63) found no significant difference in the percentage of cases of breast cancer subject of the first study: breast cancer came to 1.5% (N = 46) of the cases treated with placebo and 1.8% (n = 57) in cases treated with alendronate (hazard ratio [HR], 1.24 [95% CI, 0.84 to 1.83]). The analysis of the study showed no significant difference: 0.8% (n = 29) in the placebo group and 0.9% (n = 33) in the group treated with zoledronic acid (HR, 1.15 [95% CI, 0.70 to 1.89]). A significant difference was detected even when data from FIT and HORIZON-PFT were grouped, HR, 0.20 (95% CI, 0.89 to 1.63). So the two important randomized clinical trials do not support the results of observational research and in contrast to the results of the latter, it has been shown that 3 or 4 years of treatment bisphosphonates do not reduce the risk of invasive breast cancer in post-menopausal (63). Furthermore, other observational studies have suggested a possible protective effect of bisphosphonates on colorectal cancer (CRC), with 30-40% reduction in risk, even in the absence of randomized clinical studies (64-66), including women Health Initiative (67). However, the review of cases Women’s Health Initiative showed that the association between the use of oral bisphosphonates and risk of CRC has not reached statistical significance (HR 0.88). Furthermore, there was no evidence greater reduction in risk for women who had used the plus BF. The explanation of the different conclusions of previous studies could be achieved in the presence of confounding factors not controlled in several studies (68).

Alendronate (AL)

Notoriously this drug effectively reduces the risk of vertebral fractures in postmenopausal women in the presence or absence of pre-existing vertebral fractures, as has long been demonstrated in the Fracture Intervention Trial (FIT) (69, 70). AL reduces bone resorption and increases BMD already at a dose of 5 mg daily in patients 60 years of age, where determines 3.5% increase in BMD at the lumbar spine and 1.9% at the level of hip (p <.001 compared to baseline in both sites) (71) and total body BMD (72). The long-term extension of the study FIT for ten years in total treatment, shows that the increase in BMD lasts both at the level of the lumbar spine in which the femoral level and this causes a persistent reduction in the risk of fracture (70).

In addition to the data from bone biopsies performed in patients treated with AL for ten years, It found in all the samples of biopsy, double-tagged with fluorescent tetracycline, indicating that bone remodeling continues even during treatment. Thus, also assuming AL does not determine a framework of bone “frozen” (70). These data are reassuring with respect to the ability of alendronate to reduce safely and long-term events in fracture vertebral and non.

The efficacy of alendronate 5 mg calcitriol 0.5 mg / day administered to 98 postmenopausal women with HR-positive breast cancer treated early with AI, was evaluated in a double-blind, randomized, placebo-controlled, prospective and conducted for
24 weeks (73). At baseline and at 24th week were measured bone mineral density (BMD) and bone turnover markers. The difference in lumbar BMD between the groups was 3.0% (p <0.005). Although there was an increase of C-telopeptide after 24 weeks of therapy, this was significantly lower than in the group treated with AL and vitamin D than those treated with placebo (35.2 ± 17.5 vs 109.8 ± 28%, 6%, p <0.05). The study therefore demonstrates that a combination of 5 mg of alendronate and 0.5 mcg calcitriol is effective for preventing the bone loss induced by Al.

**Risedronate (RIS)**

It has long been known that this preparation preserves bone mass and preserves bone microarchitecture (74). Studies in postmenopausal women showed that risedronate significantly reduces the risk of vertebral fractures similarly and non-vertebral (75, 76). Already at a dose of 5 mg daily risedronate reduced the incidence of new vertebral fractures in the 1-year treatment (75, 76). The reduction in the risk of new fractures is maintained up to a total of 7 years of treatment (77). This drug, used for 3 years, has also reduced the risk of hip fractures as it emerges from a study of 9331 elderly women at high risk of fracture (74). Furthermore, treatment with 5 mg daily for 2 years, administered to postmenopausal women recently pointed out that compared with placebo, this assay determines increase of more than 5% of BMD of the lumbar spine (p <0.05 compared to baseline and placebo) (78). So there is evidence that risedronate prevents bone loss and preserves trabecular architecture when used in the first months of menopause (79). Moreover, the reduction in the risk of vertebral fractures is an independent parameter by increased BMD (74). A study was conducted with the use synchronous in postmenopausal women, anastrozole taken as adjuvant therapy for early breast cancer and risedronate. Evaluating the effects of the latter on BMD and bone turnover (80). After the first six months of care Drug Association, was performed the analysis of bone turnover markers. The obtained data were stratified according to risk at time 0, vertebral fracture and hip. A load of the lumbar spine, the level of risk has been defined by a T-score of -2 or by a history of fracture, or in the presence of both of these conditions. Risk “Mild” included patients with a T-score of less than 1, but greater than or equal to -2. The “Low” risk included T-score patients with a score equal to or greater than -1. The subjects defined high-risk received therapy with anastrozole and risedronate 35 mg administered weekly. The cases defined at moderate risk were randomized double-blind to receive anastrozole and risedronate or placebo. The cases with lower risk, received anastrozole and an integration with calcium and vitamin D. All cases in the study showed a significant increase in serum CTX (p = 0.05), demonstrating an increased bone resorption. Conversely, in no case has been a significant change in the indices of neoformation, P1NP or bone ALP. All subjects at higher risk, treated with anastrozole and risedronate 35 mg administered on a weekly basis, have shown significant change of all bone markers (p <0.0001). In the moderate-risk group, patients treated with anastrozole and risedronate, have significantly reduced all the markers of bone turnover, compared to patients treated with anastrozole and placebo (p <0.0001). Therefore, the study concluded that the administration of 35 mg week of risedronate is able to reduce bone turnover in postmenopausal women with estrogen receptor positive that are treated with anastrozole, even in the presence of a pre-existing moderate risk or high fractures (80). Oral administration of bisphosphonates to the dosage used for postmenopausal osteoporosis in the study SABRE (80) has proven effective in maintaining bone health in women treated with anastrozole. In the study SABRE was not observed bone loss, whereas in the placebo-treated patients there was a reduction in BMD in subjects with low and medium risk of fractures (80).

**Ibandronate**

The ARIBON is a double-blind, randomized, placebo-controlled study to evaluate the impact of treatment with ibandronate on BMD of 131 women treated surgically with early breast cancer in two centers in the UK. Its use in monthly administration at a dose of 150 mg (81), has also proved effective in maintaining bone health in women treated with anastrozole. Of these, 50 patients had osteopenia (T-score -1.0 to -2.5) at the hip that the lumbar spine before starting treatment. All patients were treated with anastrozole 1mg once of and supplementation with calcium and vitamin D. Patients were randomized osteopenic to receive treatment with ibandronate 150 mg orally every month or placebo. After 2 years, patients treated with ibandronate osteopenic have reported an increase in BMD at the spine (+ 2.98%) and the hip (+ 0.60%). Conversely, the patients treated with placebo had seen reduced BMD of the spine (-3.22%) and femur (-3.90%). The differences between the two treatment arms were then statistically significant. In both sites (p <0.01), after twelve months, the c-telopeptide urine, the c-telopeptide and plasma levels of bone alkaline phosphatase in plasma were decreased in patients treated with ibandronate (30.9, 26.3 and 22.8%, respectively), with an increase in those treated with placebo (40.3, 34.9, and 37.0%, respectively).

**Zoledronic acid (AZ)**

Zoledronic acid is the most powerful among the bisphosphonates available (82, 83). It contains two nitrogen atoms in the side chain. At a dose of 5 mg per year, is used in the prevention and treatment of osteoporosis with fracture and for the treatment of Paget’s disease. Zoledronic acid has been approved by regulatory agencies for the prevention of postmenopausal osteoporosis. In a case study of 351 postmenopausal women with low BMD, administering zoledronic acid or placebo was observed a significant reduction, dose-dependent markers of bone resorption, as well as a significant improvement in BMD in the different treatment groups compared to placebo (84). Even using a dose of 4 mg per year, were detected changes in markers of bone turnover similar to that observed by administering an oral bisphosphonate (85). Furthermore, it was approved for the prevention and treatment of bone metastases, cancer-induced hypercalcemia of where is administered intravenously at a dose of 4 mg every month. Recent studies show efficacy data in the prevention and treatment of osteoporosis AI-induced. Zometa-Femara Adjuvant Studies Synergy (Z-FAST) and ZO-FAST) have shown that zoledronic acid administered at...
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A dose of 4 mg infusion every two years in patients treated with letrozole has significantly improved bone mass even with normal BMD at baseline (86, 87). The most significant data on reducing the risk of fracture induced by zoledronic acid, are those of the study HORIZON-PFT (Reclast Health Outcomes and Reduced Incidence with Zolendronic Acid Once Yearly-Pivotal Fracture Trial). In this study, a similar scheme is used, with zoledronic acid for a treatment period of 3 years, followed by 3 years of placebo or active extension with the medicine. This is a landmark study to evaluate the incidence of fractures in men and women of average age 50 years or older individuals who had already suffered a minimal trauma fracture (88). The study data show that zoledronic acid given for 3 years reduced by 70% the risk of vertebral fractures, compared with placebo (RR: 0.30; 95% CI: 0.24 to 0.38). So the study HORIZON confirms a reduction in the incidence of morphometric vertebral fractures with an odds ratio of 0.51 (95% CI, 0.26 to 0.95). In addition, previously had been detected in the group treated with zoledronic acid, increase in BMD and a trend to a loss of height that was less than those treated with placebo (89). However, the study HORIZON not report a significant reduction in non-vertebral fractures.

In another study, 301 patients with breast cancer receiving adjuvant letrozole were randomized to use immediately after the start of this therapy, or after some time, zoledronic acid administered intravenously at doses of 4 mg each 6 months (90). After two doses, in the group that started early therapy, lumbar spine BMD was significantly changed, with an increase of 4.4% compared to the group that started treatment late. At the same time in the first group, the markers of bone resorption were reduced by 15% (90).

Other advantages of bisphosphonate therapy

BP can prevent complications of bone metastases in breast cancer (pamidronate, ibandronate, ZA), in prostate cancer (clodronate, ZA), lung (ZA), kidney (ZA), thyroid and bladder (ZA), also in colorectal cancer (ibandronate) and multiple myeloma (clodronate, ZA). In all these cases the BF also act on the control of bone pain, reducing the need to take opioids and leading a positive impact on quality of life (91).

Since BP are strong inhibitors of osteolysis, may limit the invasion and survival of tumor cells in the bone marrow, by changing the microenvironment.

Contributing to apoptosis of malignant cells, the BP act synergistically with anti-neoplastic. This was detected with chemotherapy associated with use of clodronate, ZA, ibandronate and hormone therapy associated with clodronate and ZA.

Even during therapy with radionuclide was used in radiotherapy ZA and pamidronate, ibandronate and ZA. Furthermore, by combining BP and radiotherapy, the clinical benefits are such as to increase bone mineral density, increasing also the re-calcification of the area involved. In patients with breast cancer and prostate cancer treated with hormone therapy (androgen deprivation or anastrozole, respectively), are reduced morbidity and osteopenia related to anti-neoplastic using pamidronate, clodronate, ZA, RIS and AL (91).

While suspecting the possibilities, there is not enough clinical evidence to confirm a potential anti-tumor effect of ZA, requiring additional clinical trials to demonstrate this effect (92, 93).

The indication for use of BP should always be evaluated even when the patient moans pain or is at an early stage of the disease (94) because BP could have the important significance of maintaining bone health in patients with neoplastic disease and represent a complementary treatment for those in advanced stages (95).

Canadian guidelines recommend the use of bisphosphonates in men with osteoporosis or in the presence of fragility fractures (96) and in patients treated with ADT (97).

Not too long there is a growing awareness of the deleterious effects of ADT and bone are available evidence of effectiveness of bisphosphonates in patients with prostate cancer.

For a long time the prescription of an early bone mineral density and the use of a treatment to prevent the events induced by bone cancer therapies have been taken into account.

Examining the percentage of prescriptions for bisphosphonates in males at the beginning of treatment with ADT in Ontario between 1995 and 2012, it was noted that the requirements of bisphosphonates in men receiving ADT were scarce during the study period, even for cases at higher risk of fracture. This suggests that there is a limited awareness among clinicians regarding the optimal management of bone health in cancer patients.

Incidentally, in Canada after 2009 there was also a decrease in prescriptions for bisphosphonates, and probably at least partly because of the negative media campaign on the association between the use of bisphosphonates, osteonecrosis of the jaw and fractures atypical femur (98). Moreover, recently Stachnika et al. (99), emphasize the possibility of proposing bisphosphonates in the prevention and treatment of lung cancer and other cancers, including breast cancer HER family-driven cancers, cancers of the colon, stomach, and head/neck.

In fact, it has been shown that bisphosphonates can inactivate the receptor of the human epidermal growth factor (HER) family of receptor tyrosine kinases (RTK) (100). The BF bind directly to 1/2 kinase domain HER1 and inhibiting downstream signaling, are able to reduce cell viability in HER-driven lung, breast, and colon (100). So there would be a selective action of bisphosphonates in these four HER isoforms of malignant disease by this route (100).

The demonstration of this new mode of action of BP, could explain the reduced spread of cancer cells and the increase in disease-free survival documented in early (42, 101).

Furthermore, this knowledge may also explain the epidemiological observations from which it is shown that patients taking oral BF for the treatment of osteoporosis had a lower incidence of colon cancer and breast cancer (66, 102).

Possible disadvantages of bisphosphonate therapy

The great advantages of therapy with oral bisphosphonates are definitely ease and autonomy of administration and good tolerability profile.

The most common side effects associated with this mode of administration are abdominal pain and dysphagia. Moreover, by randomized controlled trials conducted to date, alendronate showed gastrointestinal side effects compared to placebo (103).

The intravenous administration of bisphosphonates offers other advantages such as a lower frequency of administration and a reduced percentage of gastrointestinal side effects than the oral route.

With regard to the risk of osteonecrosis of the jaw or maxilla, which documented potential and rare complication of the use of bisphosphonates (104) should make some important consid-
Osteonecrosis of the jaw (ONJ) is an avascular bone necrosis that, regardless of the use of BP may still occur in cases at higher risk for this condition. The condition that most increases the risk of ONJ, the most commonly reported, is the dental surgery and in particular the tooth extraction (85).

Furthermore, most of the report shall refer the association to frequent doses of bisphosphonates in high doses intravenously and in particular, pamidronate and zoledronic acid in cancer patients with a history of breast cancer or myeloma. Many of these cases had already executed previously and concurrently chemotherapy or radiotherapy, or both, therapies that are already in themselves risk factors for avascular bone necrosis.

Studies and clinical reports refer ONJ with the use of alendronate and risedronate (104). However, no clinical study to date reported cases of ONJ and this is an important finding given that total clinical observation involved about 100,000 patients treated with bisphosphonates for an average of 3 years. In a retrospective review of medical records of “Cancer MD Anderson Center” in 4000 cancer patients receiving zoledronic acid or pamidronate or both, ONJ has been described in the 0.825% of the cases treated (105).

In the HORIZON PFT, the incidence of ONJ was similar in the treatment groups and the placebo group of the cases was validated one for each group. Since 2003 are reported around the world, no more than 50 cases per year, with an annual average of one case per 100,000 treated subjects.

There are recommendations to the ONJ associated with bisphosphonate therapy in patients with osteoporosis product jointly (2009), from National Association of Italian Dentists - ANDI, and the Italian Society Diseases by the Italian Society of Osteoporosis, Mineral Metabolism and Disease in the skeleton - SIOMMMS- recognizing ONJ to a low level of evidence, according to evidence-based medicine (EBM) but with a high level of recommendation (evidence level VI, grade of recommendation a) (106).

The current international guidelines, recognize ONJ as a very rare condition limited especially to the population oncology receiving high doses of intravenous bisphosphonates. It would need to have prospective data in oncology population and not only to better understand the pathophysiology of ONJ, in order to take appropriate decisions on the prevention, diagnosis and management of this disease. Indeed, the use of intravenous formulations has proven particularly effective in the management of skeletal complications in patients with cancer, taking due account of the advantages of intravenous bisphosphonates are far superior to the risk of developing ONJ. Additional data obtained from prospective studies are needed to understand the real incidence and pathophysiology of ONJ.

In addition, the annual dose therapy for osteoporosis is significantly lower than that used in subjects with cancer.

**RANKL inhibitors: denosumab**

Osteoprotegerin (OPG) acts as a decoy receptor for RANK, interrupting osteoclast activation and bone resorption. Essentially, denosumab acts just like OPG and RANKL by Occupying Preventing it from binding to RANK.

Denosumab is a monoclonal antibody of human RANK, human acts on bone loss related to the tumor, preventing the activation of osteoclast activity and subsequently reducing bone resorption. A phase II study shows that denosumab was well tolerated and had a similar effect on bone turnover to that of alendronate (107). Compared with patients receiving placebo, those treated with denosumab had a significant increase in BMD. Subcutaneous administration of the drug in doses of 30 mg every 3 months, or 60 mg every 6 months, determined the reduction urinary excretion of N-telopeptide (107). In addition, denosumab was shown to effectively reduce bone turnover in patients with metastatic similar to intravenous pamidronate. This study examined the relationship between OPG and bone loss in women with chemotherapy induced ovarian failure (COFO). In what was likely a compensatory response to rapid bone loss, COF patients’ OPG levels increased at 6 months and then decreased at 12 months to values greater than baseline assessments. This phenomenon is described in other diseases, but never before in COF. The protective effect of OPG against bone loss has been extensively studied in mice. Mice that exhibited high levels of OPG had increased bone density (108). If the OPG was removed, mice developed early osteoporosis (109). It was found that it prevented bone resorption and maintained mineralization (110).

In one meta-analysis, we pooled data from 11 studies. Based on the results of statistical analysis, we concluded that there was no significant difference in AAE, SAE, neoplasm/cancer and deaths between denosumab and control group. Compared to placebo, denosumab treatment significantly reduced the risk of non-vertebral fracture but increased the risk of SAE related to infection in the postmenopausal women with osteoporosis or low BMD. However, there was no difference between the safety of denosumab and bisphosphonates. Denosumab is a valuable new option for the treatment of postmenopausal osteoporosis in women and may be used as a first-line treatment in future. However, due to the existence of the unstable factors, furthermore studies need to be done to verify the result of this study (111).

These studies in mice eventually led to the development of a new targeted therapy, denosumab (Prolia®), which was approved by the FDA for use in postmenopausal osteoporosis in 2010 (112) and for use in metastatic bone disease (113-115).

Smith et al. (116) conducted a double-blind, randomized, placebo-controlled study of subjects which for 36 months took on androgen deprivation therapy for prostate cancer without metastases, the effects of a synchronous use of denosumab at a dose half-year 60 mg subcutaneously and a daily supplement of at least 1000 mg of calcium and at least 400 IU of vitamin D were studied. The patients were undergoing androgen deprivation therapy with bilateral orchectomy or treatment with GnRH-agonist administered for at least 12 months. Patients, of which about 60% completed the study (expected duration 36 months), had a baseline BMD T-score <-1 in the lumbar spine, total hip or femur, or neck, or a history of an osteoporotic fracture. After 24 months of therapy, the BMD of the lumbar spine increased by 5.6% compared to baseline in the group treated with denosumab, while the placebo group had a loss of 1.0%. Increased values of BMD were also observed at the total hip, femoral neck and distal third of the radius. In the group treated with denosumab, biochemical markers of bone turnover were significantly decreased compared with placebo. After 36 months, patients treated with denosumab had a significant reduction in the incidence of new vertebral fractures (1.5%, compared to 3.9% with placebo) (RR, 0.38; 95% CI, 0.19-0.78; p = 0.006). Another randomized, placebo-controlled, with BMD as the endpoint, was conducted in men with low BMD and treated with denosumab at a dose 60 mg subcutaneously every 6 months for 1 year, associated with daily supplements of calci-
um and vitamin D, in a study (117). The inclusion criteria of the study, which included 242 men aged between 30 and 85 years (mean 65), provided for a T-score between ≤2.0 and ≥3.5 at the lumbar spine or femoral neck or a previous major osteoporotic fracture and a T-score ≤ -1.0 and ≥3.5 at the lumbar spine and femoral neck. After 12 months of treatment with denosumab, the lumbar spine BMD was significantly increased compared to placebo, 5.7% at the total hip by 2.4%, and 2.1% at the femoral neck.

Studies of denosumab in the male did not show any kind of security problem. Possible side effects rare but serious with denosumab, include hypersensitivity reactions potentially serious, severe hypocalcemia, osteonecrosis of the jaw and atypical femur fracture.

**Discussion and conclusion**

A large cohort of cases of breast cancer survivors, initially treated with AI, shows that 11.2% of them had a history of osteoporosis in 16.4%, with fractures in 4.6% even before the diagnosis of breast cancer (32). Although the majority of postmenopausal women have been treated early with AI, a significant proportion of them (13.8%) had been previously treated with TAM. In these subjects TAM, compared with patients treated immediately with AI, osteoporosis was detected in almost twice as many cases probably this observational study has the largest case series to date in describing the use of AI as primary hormone therapy associated with increased morbidity bone (32). An earlier study of 343 patients with early breast cancer and about to start therapy AI, noted the presence of osteoporosis in 22.2% of cases and the presence of a fracture in any district in 11.4% of cases (20). Another study conducted on 497 patients with breast cancer took over, the time of initiation of treatment with AI that 19.1% of cases had non-vertebral fractures (118). Compared with the results of the prevalence of osteoporosis and fractures in 11.2% in 16.3%, Servitja et al. (20) reported a higher rate of osteoporosis and also a lower rate of fractures compared to the data of Bouvard et al. (118) who report a higher rate of fractures. So if you notice a history of osteoporosis, this could influence the selection of the first hormonal therapy in patients at low risk of recurrence. Furthermore, the presence of risk factors for osteoporosis or the presence of fractures before the diagnosis of breast cancer are quite similar to those of the healthy elderly (119), potentially severe hypersensitivity, severe hypocalcemia, osteonecrosis of the jaw and atypical femur fracture.

**Recommendations for maintaining bone health in cancer patients**

A significant proportion of breast cancer patients treated with AI, or in men receiving ADT for prostate cancer, they do not receive information on the screening of osteoporosis with a BMD measurement, evaluation of which should increase the awareness of its importance in cases destined to see increased their risk of fracture. Because the oncologist cares primarily for the care of the cancer but not the induced osteoporosis, measurement of bone mineral density is not required on a regular basis even if this is a method of easy execution and not invasive. Often, the administrative regulations in force in the regions, does not provide for the possibility prescriptive (if not paid by the patient), which is not included with the neoplastic therapies for its management, among the criteria.

In a Consensus Paper of the Belgian Bone Club (120), shows indications concerning the management of bone health in men and women respectively treated for prostate cancer and breast cancer (Table 3). But since most of the available clinical trials reveal that therapies to treat breast cancer induce significant changes in bone turnover besides BMD and fracture risk, in particular, with the use of the preparations of the third generation aromatase inhibitors, most scholars recommend to all women undergoing surgical castration or other therapies that cause depletion of estrogen, an early assessment of the risk of osteoporosis (121).

These subjects should perform an early bone density scan that measures the mineral density (BMD) by X-ray absorptiometry dual energy absorptiometry (DEXA).

In patients prior hormonal ablation, who are in a state of osteopenia or osteoporosis, you should also consider the additional notes and conditions that worsen the health of the skeleton, such as vitamin D deficiency, hyperparathyroidism, hyperthyroidism and hypercalcemia in relation to the values of BMD measured, if the BMD score is ≤-2.5 or lower, or there is a reduced BMD (T-score between -1 and -2.5) and coexisting factors of increased risk of fragility fractures, should be indicated a bisphosphonate therapy or with denosumab.

However, to date there has been defined the optimal duration of bisphosphonate therapy. Surely it is logical to think that this therapy should be conducted at least throughout the period in which it is conducted therapy with aromatase inhibitor (121). A panel of experts addressed the issue of skeletal effects of AIs and effectiveness of anti-fracture therapies for the prevention of AI-induced bone loss and fractures. Recommendations by national and international organizations, and experts’ opinions on this topic were evaluated.

The working group ESCEO (2012), recommends that all women treated with AI should be assessed for their risk of fracture. In these cases apply, then the general recommendations for the reduction of risks. Furthermore, it is recommended the use of zoledronic acid 4 mg intravenously every 6 months, or 60 mg of denosumab sc, or the use of oral bisphosphonates, administered for the entire period of treatment AI definitely in all cases with osteoporosis (T-score hip / spine <-2.5 or ≥ 1 prevalent fragility fracture), in women aged ≥ 75 regardless of baseline BMD, and in cases with T-score between <1.5 ± 1 with a clinical risk factor or a T-score <-1.0 ± 2 and with more clinical risk factors. Alternatively, therapy may be considered in patients with hip fracture probability ≥ 3% at 10 years, through the evaluation of the algorithm FRAX (122).

Guidelines on the prevention and treatment of bone fragility in patients with recurrent cancer non-metastatic prostate cancer treated with androgen deprivation therapy (ADT), also have the recommendation to perform before the ADT and bone mineral densitometry subsequently initiating treatment with bisphosphonates (123). The goal of treatment is to prevent (new) fractures and interventions to reduce the risk of fracture should be aimed mainly at those men at substantial risk of fracture. Advanced age, a history of prior fractures after age 50, and a low BMD are the main risk factors for fractures in men, with the contribution of additional independent clinical risk factors. To use a combination of these risk factors to assess the risk of fracture is the preferred approach to identify men at high risk of fracture likely to benefit from treatment have been proposed other methods that combine risk factors and estimate the odds fracture in absolute, such as the FRAX® algorithm (122) and the monogram Garvan (124).
Table 3 - Recommendations adapted from management of cancer treatment-induced bone loss in early breast and prostate cancer – a consensus paper of the Belgian Bone Club (120).

Measurement of bone mineral density (BMD) by DEXA and evaluation of specific risk factors for osteoporotic fractures in all patients.

BMD monitoring every 1-2 years in the presence of osteopenia and osteoporosis.

BMD monitoring every 2-5 years in patients with normal BMD at time 0, in the presence of other risk factors.

Recommend changes in lifestyle and adequate intake of calcium and vitamin D.

Recommend changes in lifestyle and adequate intake of calcium and vitamin D.

- Patients with osteoporosis (T-score < -2.5 or a history of fragility fractures).
- Patients osteopenic (T-score between -1.0 and -2.5) in view of the severity of osteoporosis and the simultaneous presence of other risk factors.

Regular measurement of BMD in untreated patients before the beginning of therapy, if there is significant bone loss in osteopenic patients.

References

1. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. Lancet. 2011;377:1276-1287.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer Statistics, 2014 CA. Cancer 2014;64:9-29.
3. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013;132(5):1133-1145.
4. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, Cronin KA. US incidence of Breast Cancer Subtypes Defined by Joint Hormone Receptor and HER2 Status. J Natl Cancer Inst. 2014;106:5. doi:10.1093/jnci/dju055.
5. Cho SH, Cho SH, Lee JA, Moon H, Kim DS. Reduced spinal bone mass in patients with uterine cervical cancer. Obstet Gynecol. 1991;78:689-92.
6. Hung YC, Yeh LS, Chang WC, Lin CC, Kao CH. Prospective study of deceased bone mineral density in patients with cervical cancer without bone metastases: A preliminary report. Jpn J Clin Oncol. 2002;32:422-4.
7. Stavraka C, Maclaran K, Gabra H, Agarwal R, Ghaem-Maghami S, Taylor A, Dhillon WS, Panay N, Blagden SP. Gynecologic Oncology: A Study to Evaluate the Cause of Bone Demineralization in Gynecological Cancer Survivors. The Oncologist. 2013;18:423-429.
8. Pleischfner J, Diel J. Osteoporosis Due to Cancer Treatment: Pathogenesis and Management. J Clin Oncol. 2000;18:1570-1593.
9. Michaud LB, Goodin S. Cancer-treatment induced bone loss, part 1. Am J Health Syst Pharm. 2006;63:419-430.
10. Howland WJ, Leoffler RK, Starchman DE, Johnson RG. Postirradiation atrophic changes of bone and related complications. Radiology. 1975;117:677-8.
11. Oh D, Huh SJ, Nam H, et al. Pelvic insufficiency fracture after pelvic radiotherapy for cervical cancer: analysis of risk factors. Int J Radiat Oncol Biol Phys. 2008;70:1183-8.
12. Mundy GR, Elton G, Orr W, Sprio TP, Yoneda T. Osteoclast activating factor: its role in myeloma and other types of hypercalcemia of malignancy. Metab Bone Dis Relat Res. 1990;2:173-7.
13. Stewart AF, Vignery A, Silverglate A, et al. Quantitative bone histomorphometry in humoral hypercalcemia of malignancy: Uncoupling of bone cell activity. J Clin Endocrinol Metab. 1982;55:219-27.
14. Henderson JE, Shustik C, Kremer R, Rabban S, Hendy GN, Gottzman D. Circulating concentrations of parathyroid hormone-like peptide in malignancy and in hyperparathyroidism. J Bone Miner Res. 1990;5:105-13.
15. Suva LJ, Winslow GA, Wittenhall RE, et al. A parathyroid hormone-related protein implicated in malignant hypercalcemia: Cloning and expression. Science. 1987;237:893-6.
16. Seyberth HW, Segret GV, Morgan JL, Sweetman BJ, Potts JT Jr, Oates JA. Prostaglandins as mediators of hypercalcemia associated with certain types of cancer. N Engl J Med. 1975;293:1278-83.
17. Nishio K, Tanabe A, Maruoka R, et al. Bone mineral loss induced by anticancer treatment for gynecological malignancies in premenopausal women. Endocr Connect. 2012;2:11-7.
18. Hwang JH, Song SH, Lee JK, Lee NW, Lee KW. Bone mineral density after concurrent chemoendocradiation in patients with uterine cervical cancer. Menopause. 2010;17:416-20.
19. Kwan ML, Ambrosone CB, Lee MM, Barlov J, Krahthwohl SE, et al. The Pathways Study: a prospective study of breast cancer survivorship within Kaiser Permanente Northern California. Cancer Causes Control. 2008;19:1065-1076.
20. Servitja S, Nogues X, Prieto-Albarran D, Martinez-Garcia M, Garrigos L, et al. Bone health in a prospective cohort of postmenopausal women receiving aromatase inhibitors for early breast cancer. Breast. 2012;21:95-101.
21. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma; suggestions for a new method of treatment with illustrative cases. Lancet. 1896;2:104-107.
22. Rao TL, Huggins C. Bilateral adrenalectomy in the treatment of cancer of the breast. Archives of Surgery. 1955;71:645-65.
23. Early Breast Cancer Trialists’ Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet. 1998;351:1451-1467.
24. McCloskey E. Effects of third-generation aromatase inhibitors on bone. European Journal of Cancer. 2006;42:1044-1051.
25. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. J Clin Oncol. 2001;19:3306-11.
26. Garrett TJ, Vahdat LT, Kinn GE. Systemic adjuvant therapy of breast cancer. J Surg Oncol. 1997;64:167-72.
27. Jonat W, Kaufmann M, Sauerbrei W, et al. Goserelin versus cy-clophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: The Zoladex Early Breast Cancer Research Association Study. J Clin Oncol. 2002;20:4628-35.
28. Fogelman I, Blake GM, Blamey R, et al. Bone mineral density in premenopausal women treated for node-positive early breast cancer with 2 years of goserelin or 6 months of cyclophosphamide, methotrexate and 5-fluorouracil (CMF).Osteopores Int. 2003;14:1001-6.
29. Hong Y, Chen S. Aromatase inhibitors. Structural features and biochemical characterization. Annals of the New York Academy of Sciences. 2006;1089:237-251.
30. Geisler J, Haynes B, Anker A, Dowsett M, Lonnig PE. Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study. J Clin Oncol. 2002;20:751-757.
31. Chien AJ, Goss PE. Aromatase inhibitors and bone health in women with breast cancer. Journal of Clinical Oncology. 2008;36:5305-5312.
Prevention and treatment of bone fragility in cancer patient

32. Kwan ML, Lo JC, Tang L, Laurent CA, Roh JM, et al. Bone Health History in Breast Cancer Patients on Osteoporosis Inhibitors. PLoS ONE. 2014;9(10): e111477. doi:10.1371/journal.pone.0111477.

33. Arumugam A, Liener EA, Lakshmanaswamy R. The role of hormones and osteoporosis inhibitors on breast tumor growth and general health in a postmenopausal mouse model. Reproductive Biology and Endocrinology. 2014;12:66.

34. Pizonze R, Mininnani P, Cassina E, Pastorino F, Sismondi P. Aromatase inhibitors for breast cancer: different structures, same effects? Endocrine-Related Cancer. 2008;15:27-36.

35. Coombes RC, Kilburn LS, Snowdon CF, Pareidans R, Coleman RE, Jones SE, Jassim J, Van de Velde CJ, Delozer T, Alvarez I, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet. 2007;369:559-570.

36. Goss PE, Ingle JN, Martinos S, Robert NJ, Musa SB, Piccart MJ, Castiglione M, Tu D, Shepherd LE, Pritchard KI, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst. 2005 Sep 7;97(17):1262-71.

37. ATAC Trialists’ Group. Results of the ATAC (arimidex, tamoxifen, alone or in combination) trial after completion of 5 years’ adjuvant treatment for breast cancer. Lancet. 2005;365:60-62.

38. Coates AS, Sahmavari A, Thurlimann B, Mouridtsen H, Mauriac L, Forbes JF, Pariandes R, Castiglione-Gertsch M, Gelber RD, Colleoni M, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. Journal of Clinical Oncology. 2007;25:486-492.

39. Geisler J, Lennig PE, Krag LE, Lokkevik E, Risberg T, Hagen AI, Schlichting E, Lien EA, Ofjord ES, Eide GE, et al. Changes in bone and lipid metabolism in postmenopausal women with early breast cancer after terminating 2-year treatment with exemestane: a randomised, placebo-controlled study. European Journal of Cancer. 2006;42:2968-2975.

40. Goss PE, Qi S, Cheung AM, Hu H, Mendes M, Pritchett KP. Effects of the steroidal aromatase inhibitor exemestane and the nonsteroidal aromatase inhibitor letrozole on bone and lipid metabolism in ovariec-tomized rats. Clinical Cancer Research. 2004a;10:5717-5723.

41. Goss PE, Qi S, Josse RG, Pritchett KP, Mendes M, Hu H, Waldman SD, Grynspan MD. The steroidal aromatase inhibitor exemestane prevents bone loss in ovariec-tomized rats. Bone. 2004b:34:384-392.

42. Coleman R, et al. Zoledronic acid (zolodronate) for postmenopausal prevention and treatment of bone fragility in cancer patients with hormone sensitive early breast cancer: update of study 1-98. J Natl Cancer Inst. 2005 Nov 23;18(17):1864-1873.

43. Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of alendrofone on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomised clinical trial. J Clin Endocrinol Metab. 2002;87:3692-7.

44. United States, National Institutes of Health, National Cancer Institute (NCI). Study of Tamoxifen and Raloxifene (STAR) Trial [Web page]. Bethesda, MD: NCI; April 26, 2006. [Available online at: www.cancer.gov/star; cited January 1, 2008].

45. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434-41.

46. Register JY, Seeman D, Van Neerven MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab. 2005;90:2816-2822.

47. Kellner PL, Johansson H, Otten A, McLloskey EV. A meta-analysis of the effect of strontium ranelate on the risk of vertebral and non-vertebral fracture in postmenopausal osteoporosis and the interaction with FRAX® for osteoporosis. Int J Clin Pract. 2011;65(11):1233-1241.

48. Vestergaard P, Fischer L, Mele M, Mosekilde L, Christiansen P. Use of bisphosphonates and risk of breast cancer. Calcif Tissue Int. 2011 Apr;88(4):255-62. doi: 10.1007/s00223-011-9463-7. Epub 2011 Jan 21.

49. Chlebowski RT, Chen Z, Cauley JA, Anderson G, Rodabough RJ, McTiernan A, Lane DS, Manson JE, Smeteslar L, Yasmeen S, O’Sullivan MJ, Safford M, Hendrix SL, Wallace RB. Oral bisphosphonate use and breast cancer incidence in postmenopausal women. J Clin Oncol. 2010;28:3577-81.

50. Chlebowski RT, Chen Z, Cauley JA, Anderson G, Rodabough RJ, McTiernan A, Lane DS, Manson JE, Smeteslar L, Yasmeen S, O’Sullivan MJ, Safford M, Hendrix SL, Wallace RB. Oral bisphosphonate use and breast cancer incidence in postmenopausal women. J Clin Oncol. 2010;28:3577-81.
null
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2006;354:821-31.
108. Simonet WS, Lacey DL, Dunstan CR, Kelley M, Chang MS, Luthy R, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell. 1997;89(2):309-319.
109. Mizuno A, Amizuka N, Irie K, Murakami A, Fujise N, Kanno T, et al. Severe osteoporosis in mice lacking osteoclastogenesis inhibitory factor/osteoprotegerin. Biochem Biophys Res Commun. 1998;247(3):610-615.
110. Bateman TA, Countryman S. Osteoprotegerin and bone loss associated with spaceflight. Drug Discov Today. 2002;7(8):456-457.
111. Zhenyu Zhou, Chen Chen, Jun Zhang, Xinran Ji, Lifeng Liu, Guichun Zhang, Xuecheng Cao, Pingshan Wang. Safety of denosumab in postmenopausal women with osteoporosis or low bone mineral density: a meta-analysis. Int J Clin Exp Pathol. 2014;7(5):2113-2122.
112. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-765. doi:10.1056/NEJMoa0809493.
113. Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Hirsh V, et al. Randomized, double-blind study of denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377(9768):813-822. doi:10.1016/S0140-6736(10)62344-6.
114. Henry DH, Costa L, Goldwasser F, Hirsh V, Prausova J, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol. 2011;29(9):1125-1132. doi:10.1200/JCO.2010.31.3304.
115. Stoppek AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol. 2010;28(35):5132-5139. doi:10.1200/JCO.2010.29.7101.
116. Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med. 2009;361:745-755.
117. Orwoll E, Teglbjaerg CS, Langdahl BL, et al. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. J Clin Endocrinol Metab. 2012;97:3161-3169.
118. Bouvard B, Hoppe E, Soulie P, Georgin-Mege M, Jadaud E, et al. (2012) High prevalence of vertebral fractures in women with breast cancer starting aromatase inhibitor therapy. Annals of oncology: official journal of the European Society for Medical Oncology/ESMO. 2012;23:1151-1156. doi: 10.1093/annonc/mds056.
119. Lustberg MB, Reinbolt RE, Shapiro CL. Bone health in adult cancer survivors. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2012;30:3665-3674.
120. Body JJ, Bergmann P, Boonen S, et al. Management of cancer treatment-induced bone loss in early breast and prostate cancer - a consensus paper of the Belgian Bone Club. Osteoporos Int. 2007;18(11):1439-50.
121. Rozenberg S, et al. Risks of osteoporosis associated with breast cancer treatment: The need to access to preventive treatment. Maturitas. 2009;64:1-3.
122. Kanis JA, Oden A, Johansson H, Borgstrom F, Strom O, McCloskey E. FRAX and its applications to clinical practice. Bone. 2009;44:734-743.
123. Holt A, Khan MA, Gujia S, Govindasrajan R. Utilization of bone densitometry for prediction and administration of bisphosphonates to prevent osteoporosis in patients with prostate cancer without bone metastases receiving antiandrogen therapy. Cancer Manag Res. 2014 Dec 24;7:13-8.
124. Ahmed LA, Nguyen ND, Bjornrem A, Joakimsen R, Jorgensen L, Stormer J, Bluc D, Center JR, Eisman JA, Nguyen TV, Emaus N. External validation of the Garvan nomograms for predicting absolute fracture risk: the Tromso study. PLoS One. 2014 Sep 25;9(9):e107695. doi: 10.1371/journal.pone.0107695. eCollection 2014.
125. Meunier PJ, Arlot M, Chavassieux P, Yates AJ. The effects of alendronate on bone turnover and bone quality. Int J Clin Pract Suppl. 1999 Apr;101:14-7.