Prevention, diagnosis and treatment of osteoporosis following menopause induced due to oncological disease

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Summary

Owing to the improved effectiveness of the treatment protocols for oncological disease, in the last few years we have seen an increase in the number of women in iatrogenic menopause secondary to integrated oncological treatments or surgical, pharmacological or radiological therapies. Particularly if it is premature, menopause in these subjects, who are already strongly debilitated by the primary pathology, may have heavy physical and psychic repercussions on the quality of life.
Particular attention must be paid to the prevention and treatment of osteoporosis, which is linked both to premature cessation of the reproductive capacity and to the treatments for the oncological disease, which may represent an additional risk for the development of premature, severe osteoporosis. Some oncological diseases involve therapies which affect bone metabolism. At the sametime, for example in breast cancer, some bone protective drugs like hormone replacement therapy are controindicated. The introduction for breast cancer of a new category of drugs, aromatase inhibitors, seems to be linked to an increase in bone fractures.
Correct treatment of these subjects involves a multidisciplinary specialist approach which we believe can be created through a targeted menopause surgery, which would thus become the ideal place for the evaluation of problems linked to the treatment of cancer and the consequent early menopause.
A targeted surgery like this allows us to create individual treatment paths with differentiated timing, and to address questions which are still unanswered, such as the risk of osteoporosis deriving from the effects of aromatase inhibitors on the bones, and the preventive effectiveness of the combination with bisphosphonates.

KEY WORDS: bisphosphonates, oncological menopause, premature menopause, osteoporosis.

Introduction

During the last few decades, we have seen a clear increase in the number of women in iatrogenic menopause, also at a relatively young age, due to the improvement in prevention, early diagnosis and oncological treatment, particularly as regards tumours of the female genital tract. This premature menopause is a consequence of integrated oncological treatments or necessary surgical and/or radiological and/or pharmacological therapies which provoke loss of the endocrine and reproductive function.
Consequently, besides surgically-induced menopause, the problem of menopause induced by chemoantiblastic drugs and/or of ionising (Radiological and Pharmacological Induced Menopause) is becoming more and more important for the improvement of the effectiveness of the treatment protocols which allow an increase in life expectancy.
If on the one hand this has led to undoubted advantages for women's health, on the other hand, since it leads to an increase in iatrogenic menopause incidence, it creates problems because of the related clinical and therapeutic consequences. The therapeutic aim in these subjects must be to ensure a good quality of life, bearing in mind both the psychological/relational discomfort linked to the clinical condition and the high risk of sequela deriving from oestrogen deficit and from the treatments carried out, particularly often still at a young age.

Osteoporosis and oncological menopause

The problem of osteoporosis has in fact been found to be particularly important in the follow-up of these patients. As a direct consequence of treatments for oncological diseases, they may run the additional risk of developing serious, premature osteoporosis and at the same time the basic pathology, e.g. breast cancer, may constitute a contraindication for the use of hormone replacement therapy.

Effects of adjuvant endocrine treatments on bone health in breast cancer patients

Endocrine treatment in breast cancer is aimed at reducing oestrogen effects and hence in the long term may be a factor to be evaluated in determining the risk of osteoporosis in these subjects.
GnRH analogues (goserelin, tryptorelin) are used in the treatment of breast cancer in fertile age, which is characterised by receptor positivity, to produce hypogonadotropic hypogonadism.
These drugs cause significant bone mass loss, which is however reversible if the treatment is suspended. It should however be remembered that in this case the treatment protocols establish continuous long-term use for two or three years, often with a passage towards irreversible induced menopause. To date there are no data on fractures.
Tamoxifen is a selective ER modulator and is the most-used drug in the clinical management of breast cancer both in the adjuvant treatment and in the metastatic stage of the disease. In the former context is has been and still is used both as the exclusive treatment, and as treatment following on chemotherapy, with benefits which seem to be significant for all age groups.
The effects of tamoxifen on the bones would seem to depend on the patient's menopausal condition (1, 2). In pre-menopause there is a loss of bone mass, while in post-menopause there is a bone sparing effect due to the partly agonist effect of tamoxifen.
Peripheral aromatisation of the adrenal androgens or of those produced by other districts is a source of oestrogen production in

the menopausal woman. This has led to the introduction of a new category of drugs, aromatase inhibitors, which have recently gained consensus in the adjuvant setting of patients with breast cancer in post-menopause where they (particularly anastrozole) show a higher significance of action than tamoxifen in terms of reduction of relapse of the disease in the same or in distant sites. However, in follow-ups the use of this drug seems to be linked to an increase in bone fractures, particularly of the spine, due to the induction and/or exacerbation of osteoporosis, even if the amount of fractures seems to stablilise after 2 years. There are few comparative data for anastrozole versus placebo in terms of BMD or risk of fracture (3). It has been postulated that the differences between anastrozole and tamoxifen in the number of fractures observed in the ATAC study (4) are due to the fact that the inhibitor deeply suppresses oestrogen production, while tamoxifen exerts a partial agonist effect, and for this very reason cannot perhaps be an ideal drug of comparison for evaluating effect on the bones (5). However, in relation to the low oestrogen levels which are induced in these women, BMD reduction with the inhibitor does not seem to be as low as would be expected for menopause (6). The sequential administration of first tamoxifen and then an anti-aromatase agent is another strategy currently being investigated.

Regarding the administration of other molecules belonging to the category of aromatase inhibitors, use of letrozole is accompanied by an increase in reabsorption markers, and there is no compensatory increase in bone formation markers. The sequential use after 5 years of tamoxifen shows a significant increase in osteoporosis incidence with the use of letrozole as compared to placebo, but no increase in the number of fractures.

The use of exemestane has shown an increase in bone reabsorption markers but also an increase in bone formation markers, perhaps attributable to the androgenic effect of its metabolite (17 hydroxyexemestane). No differences have been shown between spinal and femur BMD as compared with placebo. In all studies the three aromatase inhibitor molecules are associated with a greater number of fractures as compared with tamoxifen or placebo.

The incidence of fractures seems lower when the inhibitor is used after treatment with tamoxifen. However, the brief period of follow-up with exemestane and letrozole complicates the interpretation of the clinical data (7, 8).

Currently the best management of endocrine response in premature breast cancer in pre-menopause still remains controversial; the benefits of aromatase inhibitors in this category of subjects are still little known. However, their use in combination with ovary suppression in women with advanced breast cancer has led to a 76% greater reduction of circulating oestrogens as compared to tamoxifen. This reduction might increase the effectiveness of the treatment, thus explaining the need to verify aromatase inhibitors in women in pre-menopause with initial breast cancer. It is a treatment whose long-term side effects are still not completely known, but there is certainly an increased risk of osteoporosis and/or fractures. This suggests the advisability of close monitoring of bone mass loss and the importance of considering the use of bone-protecting treatments in combination with aromatase inhibitors.

To date there have been no long-term studies with fractures as their primary end-point, this factor being more important for clinical purposes.

Osteoporosis treatment in female breast cancer patients in post-menopause

Oestrogen replacement therapy, the ideal treatment in subjects in premature menopause, is generally contraindicated in women with breast cancer.

Moreover, as mentioned above, because of the treatments which they undergo and the early menopause induced by chemotherapy or use of GnRH analogues, a particularly careful evaluation of the risk of osteoporosis is required for these patients.

Some studies have assessed the effect of some bisphosphonates, risedronate, clodronate and zoledronic acid, versus placebo in women with menopause induced by chemotherapy or LHRH agonists, and have shown a positive effect on these subjects' BMD (9-12).

ASCO guidelines on the use of bisphosphonates identify women with breast cancer who receive aromatase inhibitors as high-risk subjects for osteoporosis, and recommend basal assessment of BMD and consequent adjustment of treatment to the result of this assessment. On the basis of recent studies and clinical trials in progress, bisphosphonates may become the standard treatment for women with initial breast cancer (12).

Moreover evidence is emerging of the antitumoral and antimetastatic properties of zoledronic acid such as inhibition of angiogenesis and of the invasion of the bone by tumoral cells; induction of apoptosis and antitumoral synergy in combination with chemotherapy; T cell immunomodulation. Recently the addition of zoledronic acid to ovary suppression therapy with analogue plus tamoxifen or an aromatase inhibitor was seen to produce an increase in disease-free survival in subjects with initial breast cancer in pre-menopause (13).

In these subjects, a modification of life style must be recommended from the start: abolition of smoking; reduction of coffee and alcohol consumption; regular physical activity; and supplementation of the diet with appropriate amounts of calcium and Vitamin D. However, various epidemiological studies have indicated that men with calcium-rich diets may have an increased risk of more aggressive forms of prostate cancer.

The possible effects of calcium after treatment are not however known. Patients undergoing hormone-suppressing treatment are at high risk of osteoporosis, and it is not clear whether supplements of Vitamin D and calcium are useful or harmful in these cases. It may be retained prudent for patients to follow a diet containing at least 600 IU of Vitamin D per day and to consume an adequate but not excessive dose (i.e. no more than 1200 mg/die) of calcium.

Regarding raloxifen, a SERM for the treatment of osteoporosis, in Italy there are currently no indications for its use in subjects with breast cancer, even though recent studies have shown a reduction of incidence in this neoplasia (14, 15) and approved by FDA.

Phyto-oestrogens are considered a natural alternative to HRT and are commercially available as natural food supplements. Isoflavons are considered possible SERMs, but they possess non-hormonal activities which might contribute to their non-pharmacological effect. To date, the absence of controlled trials and technical controls on the extraction and creation of the preparations justifies caution in their use in patients, above all after a previous breast tumour (16, 17).

Welfare and organisational aspects of a targeted service

The consequences of prematurely-induced menopause may be very important for women who have had an oncological disease, and their treatment may present clinical and metabolic problems. Oestrogen replacement therapy (with or without combined progestins) is the most adequate treatment for the climacteric symptomatology and for the prevention of problems linked to early menopause. The choice of hormone replacement therapy must take into account the basic oncological disease, while it might be appropriate for the control of symptoms in patients with non-hormone-sensitive tumours and contraindi-

cated in those with hormone-dependent neoplasias which require alternative support treatments for the control of the climacteric symptomatology. In patients with hormone-sensitive tumours, oestrogen therapy in fact involves a theoretical risk of stimulating a relapse of the tumour, and also of increasing the possibility of other hormone-related neoplasias, with different implications depending on the type of tumour.

Correct care of these patients involves an integrated multidisciplinary approach with the coordinated intervention of various specialists (oncologist, gynaecologist, endocrinologist, psychological, etc.), and the creation of a targeted surgery. This would provide preferential access to a service with a holistic approach to the themes concerned, and which tries to reduce discomfort and give as homogeneous and exhaustive answers as possible.

From an organisational point of view, access to this welfare/diagnostic service must be facilitated by cutting down bureaucratic procedures, avoiding long periods of waiting, concentrating the controls and choosing a logistically adequate location which is seen by the woman patient as a space created specially for her, where after treatment the quality of life is discussed. At the same time it must favour collaboration between medical staff members in order to evaluate each case in its complexity and specificity, and define a strategy of intervention, apply specific protocols, carry out applied clinical research, and perhaps influence the guidelines on this specific topic.

Correct assessment, information-giving and discussion of the treatment with the female patients allows us to:

- Assess the consequences at a gynaecological/reproductive, psychological level of the adjuvant treatments and identify therapeutic paths for the prevention and solution of current and future clinical problems.
- Assess the use of HRT, where it is not contraindicated, to improve the quality of life, without any offhand exclusion of a "general cancer risk" or the possibility of alternative therapies.
- Assess the need for psychological and/or sexological consultation.
- Pay particular attention to the prevention and treatment of osteoporosis in these subjects, where early cessation of the reproductive capacity and/or the consequence of treatments undergone may have a negative effect on bone metabolism balance.

Conclusions

We believe that the creation of a targeted unit as proposed can provide both the individual and the couple with important opportunities for receiving consultation as to the consequences of cancer.

The specialised menopause surgery becomes the ideal place for the evaluation of the problems connected to treatments of the oncological disease and the consequent premature menopause.

As regards the risk of osteoporosis, the effect of aromatase inhibitors on the bones and the preventive effectiveness of the combination with bisphosphonates are two of the still unanswered questions.

It is important to assess bone metabolism in women with previous neoplasia and to see how far this is affected by the induced menopause and the tumour-related treatments. Differentiated therapeutic timing must be created for the various osteoproductive treatments according to the basic disease, the period of menopause, the age of the subject and the symptomatology.

Finally, assessment of the possible genetic influence would appear to be advisable, in terms of polymorphism for the alpha ER receptor; also the influence of aromatase on the risk of osteoporosis in these subjects, which may influence interpersonal variability in terms of bone mass and therapeutic response. This could be extremely important in clinical practice for identifying subjects at risk of the disease and in the choice of suitable treatments.

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