How to manage the menopause following therapy for breast cancer. Is raloxifene a safe alternative?

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Abstract

Raloxifene is a selective oestrogen receptor modulator (SERM) that has anti-oestrogenic effects on breast and endometrial tissue and oestrogenic actions on bone, lipid metabolism and blood clotting. In postmenopausal women raloxifene decreases bone turnover and increases bone mineral density, reducing the incidence of vertebral fractures. Unlike tamoxifen, raloxifene does not cause endometrial hyperplasia or cancer, as demonstrated by endometrial monitoring with ultrasonography and biopsy during treatment. Evidence suggests that raloxifene lowers total low-density lipoprotein cholesterol levels behaving like oestrogens, but does not increase high-density lipoprotein cholesterol levels. In randomised clinical trials on postmenopausal women with osteoporosis, raloxifene reduced the risk of newly diagnosed ER-positive invasive breast cancer by 76% during a median of 40 months of treatment. However, raloxifene does not alleviate early menopausal symptoms, such as hot flushes and urogenital atrophy, and may even exacerbate some of them. In conclusion, raloxifene may be an alternative for the prevention of long-term effects of oestrogen deficiency (osteoporosis and heart diseases) in women with previous breast cancer not having hot flushes. For symptomatic patients, the association of raloxifene with different drugs which have demonstrated efficacy in the control of vasomotor symptoms is now under evaluation.

Keywords: Raloxifene; Menopause; Breast cancer survivors

1. Introduction

Several million women worldwide have survived breast cancer, but are currently advised against the use of oestrogen for the management of menopausal symptoms and for the prevention of cardiovascular diseases and osteoporosis. Raloxifene hydrochloride is a SERM that has anti-oestrogenic effects on breast and endometrial tissue and oestrogenic effects on bone, lipid metabolism and blood clotting [1,2]. Due to these characteristics, raloxifene could be a good alternative to hormone replacement therapy (HRT) for breast cancer survivors considering prevention against osteoporosis and cardiovascular disease, as recently suggested in the Consensus Conference of Charlottesville on this issue [3].

2. Effects on bone

Clinical trials carried out in Europe and United States have demonstrated that raloxifene decreases bone turnover and increases bone mineral density (BMD) in postmenopausal women [4,5]. In the European trial, comparing raloxifene and placebo, women treated with raloxifene at different doses had a statistically significant decrease in the concentrations of the markers of bone turnover (osteocalcin, bone-specific alkaline phosphatase and ratio of urinary type I collagen C-telopeptide to creatinine) [5]. BMD increased significantly in the lumbar spine, total hip, femoral neck and total body with all doses of raloxifene, suggesting important effects on cortical as well as on trabecular bone. After 24 months, the mean increase of BMD between the group that received 60 mg/day of raloxifene and the placebo group was 2.4±0.4% for the lumbar spine, 2.4±0.4% for the total hip and 2±0.4% for the total body ($P < 0.001$ for all comparisons). A limited amount of data are available on the effects on bone quality or histomorphometry, evaluating bone biopsies before and after treatment with raloxifene; these data show no abnormalities in bone mineralisation, with no osteomalacia, cell damage, woven bone or marrow fibrosis [6]. The effect of raloxifene on the occurrence of fractures was evaluated in the MORE trial (Multiple Outcomes of Raloxifene Evaluation), a large randomised controlled trial performed in approximately 7000 postmenopasusal women [7]. At baseline, all women had osteoporosis, as determined by BMD, and some also had osteoporotic vertebral deformity. After 2 years of treatment, new vertebral fracture incidence was reduced by approximately 44% with either 60 or 120 mg/day of raloxifene compared with placebo. Risk of non-vertebral fracture for raloxifene versus placebo did not differ significantly (relative risk (RR) = 0.9; 95% confidence interval (CI: 0.8–1.1).

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3. Effects on lipids and blood clotting

Evidence suggests that raloxifene, like oestrogens, lowers total cholesterol and low-density lipoprotein cholesterol, but does not raise tryglicerides and does not increase high-density lipoprotein cholesterol levels [5,8,9]. Raloxifene also has an effect on lipoprotein(a) and on fibrinogen that could be beneficial in heart disease. However, the non lipid-related cardioprotective effects of oestrogen have not been demonstrated for SERMs and the results of a study in menopausal monkeys showed no effect of raloxifene on atherosclerosis extent in coronary vessels [10]. In summary, raloxifene has a positive effect on lipids which is probably not as strong as the effect of oestrogens, but is similar. At present, the effects of raloxifene on cardiovascular disease are unknown and are under evaluation in prospective clinical trials.

4. Effects on the breast

In experimental models, raloxifene has antiproliferative effects on breast cancer cell lines and in animal models, raloxifene inhibits the growth of ER-dependent mammary tumours induced by carcinogens [11]. The recently published results of the MORE trial, referring to 40 months of follow-up, have shown that raloxifene significantly reduces the risk of receptor-positive breast cancer among postmenopausal women with osteoporosis [12]. 13 cases of invasive breast cancer were observed in the 5129 women assigned to take raloxifene and 27 in the 2576 women assigned to take placebo (RR 0.24; 95% CI: 0.16–0.44; $P < 0.001$). Raloxifene reduced the risk of invasive ER-positive breast cancer by 90% (RR 0.10; 95% CI: 0.04–0.24), but did not influence the risk of ER-negative cancer (RR = 0.88; 95% CI 0.26–3.00) (Table 1).

As breast cancer generally requires several years to grow to a clinically or radiographically detectable size, the cancers that were diagnosed during this trial were probably already present at the beginning of the study. Therefore, the observed reduction in the risk of breast cancer within the first 40 months of treatment is probably due to suppression or regression of subclinical cancers.

Table 1
The MORE trial: incidence of breast cancer in postmenopausal women treated with raloxifene and placebo in relation to oestrogen receptor (ER) status [12]

	Placebo (%)	Raloxifene (%)	RR (95% CI)
ER+	20 (0.8)	4 (0.1)	0.10 (0.04–0.24)
ER−	4 (0.2)	7 (0.1)	0.88 (0.26–3.00)

5. Effects on the uterus

Uterine safety was assessed in postmenopausal women by endometrial ultrasound, hysteroscopy and endometrial biopsies. The effect of raloxifene on endometrial thickness and the incidence of vaginal bleeding confirms preclinical pharmacological data in animal models, showing that raloxifene blocks oestrogen-mediated uterine proliferation in rodents and does not stimulate the uterus in the ovariectomised rat model [5,7,13].

During the first 3 years of the MORE trial raloxifene did not increase the risk of endometrial cancer, but the total number of cases was small [12].

In the absence of evidence that raloxifene increases the risk of cancer or hyperplasia the routine periodic endometrial monitoring with ultrasonography or biopsy is not warranted for women taking raloxifene.

6. Adverse effects

In general raloxifene is well tolerated (Table 2). In the clinical studies raloxifene does not cause vaginal bleeding or breast pain, which often limit the use of postmenopausal oestrogen therapy. Raloxifene, tamoxifen and oestrogen increase the risk of venous thromboembolic events (VTE) to a similar degree. In the MORE trial the risk of VTE (pulmonary embolism and deep venous thrombosis) was 3.1 times higher (95% CI: 1.5–6.2) in women assigned to the raloxifene group than in those assigned to the placebo group [12]. No difference in the rate of VTE exists between the 60 and the 120 mg groups. The risk of VTE during raloxifene seems to be higher shortly after starting therapy and declines over time returning to baseline after approximately 18 months of treatment. The major problems for postmenopausal women requiring HRT are vasomotor symptoms and genital atrophy. In breast cancer survivors, hot flushes may be more frequent and severe, due to tamoxifen adjuvant treatment, chemotherapy or

Table 2
The MORE trial. Rates of adverse effects among women assigned to raloxifene and to placebo [12] clinico-pharmacological aspects of different hormone treatments

	Placebo (%)	Raloxifene 60 mg (%)	Raloxifene 120 mg (%)
Hot flushes	6.4	9.7	11.6
Breast pain	2.5	2.4	2.7
Vaginal bleeding	3.1	3.4	2.8
Influenza syndrome	11.4	13.5	13.6
Leg cramps	3.7	7.0	7.9
Thromboembolic disease	0.3	1.0	0.9
Deep vein thrombosis	0.2	0.7	0.8
Pulmonary embolism	0.1	0.4	0.3
Diabetes	0.5	1.2	1.1

luteinising hormone-releasing hormone (LHRH) analogues use [14]. The currently available SERMs including raloxifene, do not alleviate such symptoms and may even exacerbate some of them. In the MORE trial, hot flushes were reported more frequently in the raloxifene group than in the placebo group; however, only 0.6% of the women assigned to the raloxifene group compared with 0.1% of those assigned to the placebo group discontinued treatment because of hot flushes ($P < 0.001$) [12]. For symptomatic patients, the association of raloxifene with different drugs which have demonstrated efficacy in the control of vasomotor symptoms in breast cancer survivors, such as megoestrol acetate at low-doses (20–40 mg/day) and selective serotonin re-uptake inhibitors, is now under evaluation [15–17].

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Tibolone actions on normal and breast cancer cells

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Abstract

Tibolone and its main derivatives were studied in an original model of cultures of normal human epithelial breast (HBE) cells on proliferation, differentation and apoptosis, the three mechanisms responsible for breast homeostasis. Tibolone and its Δ4 isomer were antiproliferative, both in the absence and presence of oestradiol (E2). The oestrogenic 3α and 3β hydroxy derivatives did not display any mitogenic activities in HBE cells. Moreover, at 1 μM, they were antiproliferative. Tibolone and its Δ isomer increased the 17β hydroxysteroid dehydrogenase activity similarly to that observed with progestins [1]. Apoptosis was increased in HBE cells to a similar range as with the pure pregnane progestin, Org2058. We also studied the extent of apoptosis in hormone-dependent breast cancer cell lines. Tibolone and its Δ4 isomer also increased apoptosis, especially in ZR75-1 cells containing progesterone and

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