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LH-RH agonists offer very good protection against the adverse gynaecological effects induced by tamoxifen

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Abstract

This study was initiated to evaluate the efficacy of luteinizing hormone-releasing hormone (LH-RH) agonists in protecting premenopausal patients against the adverse gynaecological effects induced by tamoxifen. Between January 1998 and January 2000, 85 premenopausal breast cancer patients were included in this prospective study. All were to receive LH-RH agonists and tamoxifen for a minimum of two years. All patients underwent a pretreatment gynaecological evaluation and annual follow-up. Bone density was also measured at the start of treatment and then after 2, 3 and 4 years. Pretreatment evaluation revealed 2 polyps. At one and two years of follow-up, no abnormal symptoms were noted and echographic findings were normal. At three years of follow-up, a polyp associated with adnexal masses was discovered. Histology revealed ovarian and endometrial metastases of infiltrating lobular breast carcinoma. Bone density evaluation after 2, 3 and 4 years of treatment showed no significant bone loss. LH-RH agonists offer safe protection against the gynaecological side-effects of tamoxifen in premenopausal breast cancer patients.

Keywords: Ovarian ablation; Premenopausal breast cancer patients; Endocrine therapy; LH-RH agonists; Tamoxifen; Gynaecological side effects

1. Introduction

Many interesting questions need to be resolved regarding the exact role of ovarian suppression in the adjuvant treatment of early breast cancer [1–4]. These questions concern the use of ovarian suppression as exclusive adjuvant therapy, its synergistic action with chemotherapy and the optimal duration of this therapy [5–7]. Ovarian suppression is considered to be a valuable alternative to surgical and radiation ablation [8]. These two methods [8–10] are simple and cheap, but have the disadvantage of being irreversible and often distressing for fragile breast cancer patients. The idea of suppressing oestradiol levels, medically and temporarily, could thus be considered as a very attractive option.

The ovarian suppression induced by luteinizing hormone-releasing hormone (LH-RH) agonists is reversible [1] upon discontinuation of therapy. This property is very precious to young patients who wish to preserve their chances of bearing children several years after their breast cancer treatment. In this context, the study conducted by Williamson [11] demonstrated that goserelin inhibits follicular maturation, but not folliculogenesis. This observation corroborates the finding that, after discontinuation of therapy, many patients recover ovarian function and maintain their fertility potential.

In early breast cancer, LH-RH agonists (goserelin, Zoladex 3.6 mg monthly; Astra Zeneca, UK) and tamoxifen (Nolvadex 20 mg daily; Astra Zeneca, UK), used as adjuvant treatment for a period of 5 years, have proved

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to be a valuable alternative to cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy [2].

Nevertheless, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis has shown that the addition of adjuvant ovarian ablation to adjuvant chemotherapy [8–10] provides little benefit over chemotherapy alone. However, for young oestrogen receptor (ER)- and/or progesterone receptor (PgR)-positive patients, a preliminary report of a study by the Eastern Cooperative Group Phase III Intergroup Trial (E5188, Int. 0101) showed promising results with the addition of endocrine therapy (LH-RH agonists and tamoxifen) to cyclophosphamide, doxorubicin, 5-fluorouracil (CAF) [7].

In this regard, interesting prospective studies have now been initiated (Perche's study, Soft study, Text trial) to evaluate the benefits of endocrine therapy after chemotherapy. The combination of LH-RH agonists and tamoxifen administered for metastatic breast cancer [12,13] has also been tested in four randomised trials. A meta-analysis of these studies showed that combined endocrine therapy was superior in terms of objective clinical response, survival rates and progression of the disease [14]. Consequently, combined oestrogen blockade is now more commonly used. The aim of this study was to evaluate the gynaecological safety profile and the bone effects of LH-RH agonists used with tamoxifen.

2. Patients and methods

2.1. Patient eligibility

Between January 1998 and January 2000, 85 premenopausal breast cancer patients were included in this prospective study.

Inclusion criteria were:

1. Stage I and II breast cancer patients treated by surgery ± radiotherapy.
2. Premenopausal status confirmed by oestradiol, LH and follicle-stimulating hormone (FSH) levels.
3. Hormone-responsive tumour (ER- and/or PgR-positive).
4. If adjuvant therapy has been administered, intact ovarian function confirmed by oestradiol, LH and FSH levels before inclusion.

2.2. Treatment modalities and follow-up

All patients received an association of LH-RH agonists (Zoladex 3.6 mg monthly) and tamoxifen (Nolvadex 20 mg daily) for a minimum of 2 years after chemotherapy or for a duration of between 3 and 5 years when endocrine therapy was administered as exclusive adjuvant therapy. The variable duration was due to the fact that some patients wished to become pregnant and stopped therapy after 2 years (in the arm of endocrine therapy added to chemotherapy) or after 3 years (in the arm of exclusive endocrine therapy).

All the patients underwent a pretreatment gynaecological examination with a Papanicolaou (PAP) smear, vaginal echography, outpatient hysteroscopy and endometrial biopsy. Clinical evaluation and echography were repeated annually in the absence of abnormal symptoms, such as bleeding or abdominal pain. In case of abnormal symptoms and/or abnormal echography, defined as heterogeneous endometrium, endometrial thickness $\geqslant 5$ mm or abnormal vascularity measured by Doppler ultrasound, hysteroscopy was required. In 10 patients whose echography was normal, endometrial biopsy was performed (with their agreement) for histological and immunohistochemical studies. Bone density was also measured at the start of treatment, after 2 and 3 years and then annually. Bone density (BMD) was measured by dual-energy X-ray absorptiometry (DXA).

2.3. Statistical analysis

Bone density was characterised according to international criteria and osteoporosis was defined by a score of $\geqslant -2.5$ standard deviation (SD) below the mean value for young subjects. Bone mineral density was expressed in g/cm^2. Measurements were taken of the lumbar spine between L1 and L4 and the hip. One-way analysis of variance (ANOVA) was used to evaluate bone density. All P-values less than 0.05 were considered significant.

3. Results

3.1. Patient demographics

The mean age was 35 years with a range of 25–43 years. All patients had histologically-proven breast cancer with positive ER and/or PgR receptors. Twenty-five patients had stage I and 60 patients stage II breast cancer.

In 24 patients, endocrine therapy was the only adjuvant therapy administered following loco-regional treatment. This adjuvant therapy was decided upon by a team of oncologists and gynaecologists. Patients with stage I disease and with an endocrine-responsive tumour received this treatment in accordance with the recommendations of the St Gallen Meetings (1998, 2001 and 2003). In 61 patients, endocrine therapy was preceded by chemotherapy (stage II disease and in one very young patient with stage I disease; in all cases, they had endocrine-responsive disease). The reason we gave combined endocrine therapy after chemotherapy was that we believe, although still controversial, that very young

premenopausal patients (<40 years) could benefit from combined endocrine therapy [7]. In our study, 61 patients received chemotherapy followed by combined endocrine therapy. This combined therapy was administered in view of the good results obtained in the Intergroup 0101 study [7,8]. Ovarian function was checked in all cases and premenopausal status confirmed (Table 1). When hormonal status was in doubt, blood tests were repeated before starting combined therapy. All the patients received radiotherapy, and hormone therapy began after its completion (2.5 months after the end of chemotherapy).

3.2. Gynaecological safety

Pretreatment echographic evaluation revealed no adnexal abnormality, but 2 suspected polyps confirmed by diagnostic hysteroscopy and treated by operative hysteroscopy (endometrial resection). The histology of the 83 pretreatment endometrial biopsies and the 2 resected polyps is shown in Table 2. Histology demonstrated 31 cases of proliferative endometrium, 39 secretory, 7 dysfunctional, 6 menstrual and 2 polyps associated with simple endometrial hyperplasia.

At one and two years of follow-up, no abnormal symptoms were noted and echographic findings were normal.

At three years of follow-up, one patient complained of abdominal pain and bleeding. Echography revealed a polyp and a structure with a thick (13 mm), irregular endometrium and two heterogeneous ovarian masses of 5 cm in size. To obtain a precise diagnosis, operative hysteroscopy and laparoscopy were performed with endometrial and ovarian biopsies. The operative procedures confirmed the echographic data. Histological diagnosis revealed ovarian and endometrial metastases of infiltrating lobular breast carcinoma. A bone scan and magnetic resonance imaging (MRI) also showed bone metastases. The patient received chemotherapy with anthracyclines and, thereafter, hormone therapy with aromatase inhibitors.

At four years of follow-up, no abnormal symptoms were observed. Echography revealed, in one case, a heterogeneous 5-mm-thick endometrium, but no intracavitary lesions were noted at hysteroscopy. Biopsy showed endometrial atrophy. Atrophy of the endometrium induced by LH-RH agonists is more potent than atrophy observed after natural menopause. In the biopsies we have studied so far ($n = 10$), we have not detected any areas of proliferative endometrium in cystic glands in the endometrium of patients on tamoxifen. Results observed during follow-up are noted in Table 2 and oestradiol levels in Table 3.

Table 1
Oestradiol levels

No. of patients stratified according to age	End of chemotherapy (pg/ml)	2.5 months later	4 months later
47 patients $\leqslant 35$ years	80 (49–148)	117 (80–197)	–
12 patients 36–40 years	63 (45–126)	79 (60–132)	–
2 patients 41–42 years	38 and 29	47 and 35	69
Menstrual status	End of chemotherapy (return of menses)	2.5 months later	
47 patients $\leqslant 35$ years	43/47	47/47	
12 patients 36–40 years	9/12	12/12	
2 patients 41–42 years	0/2	1 after 2.5 months 1 after 4 months	

Table 2
Histology of pretreatment biopsies

Initial screening			
31 cases of proliferative endometrium			
39 secretory endometrium			
7 dysfunctional endometrium			
6 menstrual endometrium			
2 polyps with simple endometrial hyperplasia			
Results observed during follow-up			
Year of follow-up	Symptoms	Echography	Hysteroscopy + laparoscopy
One year	None	No abnormality	Not performed
Two years	None	No abnormality	Not performed
Three years	Abdominal pain and bleeding (1 case)	Suspected polyp and bilateral adnexal masses	Polyp and adnexal masses with histology of infiltrating lobular carcinoma (metastases)
Four years	None	One heterogeneous endometrium	No intracavitary lesions; biopsy: endometrial atrophy

Biopsies performed without abnormal signs (no symptoms and normal echography), $n = 10$.
Histology: endometrial atrophy in all cases.

Table 3
Oestradiol levels during therapy

Oestradiol levels observed during therapy	Mean value (pg/ml)	Range
At one year	21	19–34
At two years	16	12–31
At three years	12	10–17
At four years	<10	<10
Pretreatment value	115	43–299

In our study, we did not observe additional protective effects of chemotherapy on the endometrium. The only difference was the mean duration of blood loss at the beginning of the endocrine therapy. Patients not receiving chemotherapy had a mean duration of blood loss of 11 days (range: 6–18 days) and those receiving chemotherapy had a mean duration of 16 days (range: 8–25 days).

3.3. Bone density

Bone evaluation was performed before treatment, after 2 years of therapy and then annually. The *P*-values for the results are shown in Table 5. This analysis revealed no significant bone loss, even after 4 years of treatment.

4. Discussion

The recent publication by Jakesz [2] led us to consider endocrine therapy as a legitimate alternative or complement to chemotherapy in the adjuvant treatment of young women with receptor-positive breast cancer. Ongoing clinical trials (Perche, Text and Soft trials) are currently investigating the effect of ovarian ablation added to chemotherapy [6–8], or ovarian ablation as exclusive adjuvant therapy. These studies will give some indication as to the optimal scheme of endocrine therapy: ovarian ablation with tamoxifen or ovarian ablation with an aromatase inhibitor or inactivator? The aim of this study was to analyse the safety profile of the association of goserelin and tamoxifen, taking into consideration important data, such as the incidence of osteoporosis and the risk of endometrial cancer.

We did not encounter any benign endometrial pathology induced by the combined therapy. Furthermore, no cases of atypical endometrial lesions were observed. Only one case of ovarian and endometrial metastases of infiltrating lobular carcinoma was encountered in our study.

One of the advantages of using LH-RH agonists and tamoxifen in combination is preventing the intermittent spikes of oestradiol observed with tamoxifen monotherapy [15]. Although high levels of oestradiol can be associated with ovarian cysts in young women on tamoxifen, the deleterious effect of these high oestradiol levels on the prognosis of breast cancer remains a matter of debate [16–18]. Combined therapy (LH-RH agonists + tamoxifen) reduces serum oestradiol and progesterone levels to those observed after surgical oophorectomy. In our study, no peak in serum oestradiol and no ovarian cysts were observed during treatment with the combined therapy regimen. By contrast, in an unpublished study involving 89 premenopausal breast cancer patients, we observed a high incidence of ovarian cysts stratified after 12 months of endocrine therapy with tamoxifen alone (Berliere *et al.*, data not shown). In Table 4, we report the incidence rate of ovarian cysts stratified according to the patient's age and the mean oestradiol value. Recently, Moritz reported that ovarian cysts occur in over 80% of premenopausal patients treated by tamoxifen (4th Biennal International Meeting of the Flemish Gynaecological Oncology Group; January 2004).

It is usually the policy in regimen for breast cancer not to mix different types of treatment, thereby avoiding additional side-effects and/or negative interactions (ie. negative interactions between tamoxifen and chemotherapy and tamoxifen and radiotherapy). In many protocols, the combination of different treatment modalities is not permitted.

That is the main reason why in our study endocrine therapy began after radiotherapy. In addition, ovarian cryopreservation (an experimental, but promising, technique) was also proposed for our very young patients. Interestingly, Recchia [19] published encouraging data on the preservation of fertility with LH-RH ag-

Table 4
Rate of ovarian cysts and oestradiol levels in young premenopausal patients on tamoxifen alone

Age of patient (years)	Rate of ovarian cysts (%)	Mean oestradiol value (pg/ml)	Range
<35	75	950	600–1743
36–40	53	708	350–1100
41–45	51	613	380–950
46–50	48	477	180–830

Table 5
Results of bone density

	Y0	Y2	Y3	Y4
Lumbar spine				
Mean	1.1890	1.1715	1.1405	1.1270
Var	0.008	0.014	0.017	0.018
SD	0.094	0.119	0.129	0.134
P values	–	0.687	0.1823	0.1001
Hip				
Mean	1.1890	1.1575	1.1340	1.1250
Var	0.009	0.015	0.015	0.015
SD	0.094	0.123	0.121	0.122
P values	–	0.3695	0.1174	0.07222

Var, variance.

onists administered over a period of 2 years and started 2 weeks prior to chemotherapy (84% of patients recovered menses within 12 months of chemotherapy). This approach certainly needs to be investigated further.

LH-RH agonists seem to be more efficient than "natural menopause" at overcoming the oestrogenic agonistic effects of tamoxifen on the endometrium [20]. In our previous study, postmenopausal patients (experiencing natural menopause or menopause induced by surgical ablation) developed benign and atypical lesions induced by tamoxifen. In this trial, 510 postmenopausal patients were prospectively enrolled. On the basis of the pretreatment gynaecological screening, patients were divided into two groups: (1) patients without initial endometrial lesions (425 patients), (2) patients with initial endometrial lesions (85 patients).

During tamoxifen therapy (5 years) and for one additional year, patients were followed annually; the duration of follow-up was therefore 6 years. The incidence of benign endometrial lesions was 13.6% in group 1 and 18.8% in group 2 (no significant difference). By contrast, the incidence of atypical lesions was 0.7% in group 1 and 14% in group 2 ($P < 0.05$). That is why we believe that pretreatment screening is important for patients receiving tamoxifen therapy to determine their risk factors, such as pretreatment lesions, obesity and other classical risk factors linked to unopposed oestrogen therapy [20,21].

To try to explain the remarkable protection of the endometrium effected by goserelin, we are now studying the immunohistochemical profile of endometrial biopsies collected from women on combined therapy to compare the results with endometrial data from women on tamoxifen alone [22–24]. Exact mechanisms implicated in this process remain unexplained, but we know that LH-RH agonists have already been studied in metastatic or inoperable endometrial cancers, with some degree of success [25].

Only 2 small prospective studies have described the use of LH-RH agonists as primary treatment of several types of endometrial hyperplasia [26,27]. In the study by Grimbizis and colleagues, five patients presented with complex atypical hyperplasia and were treated for 6 months with LH-RH agonists. Two patients experienced a regression of the disease to complex non-atypical hyperplasia and two patients exhibited a normalisation of the endometrium to atrophic endometrium. However, in one patient, complex atypical hyperplasia persisted after 6 months of treatment. In the study conducted by Jadoul and Donnez [28], similar results were observed. Although these series were small, the results are promising [28].

The antiproliferative activity of LH-RH agonists probably involves different mechanisms [25,28–30]. Direct cytotoxicity and blockade of growth factors have been proposed. An interesting concept is the hormonal control of apoptotic cell death by LH-RH agonists. According to data published by Imai's team [31–33], this mechanism is mediated by the Fas and Fas ligand system [29,30] and has been studied in hormone-dependent tumours, such as breast, ovarian and endometrial cancers. Direct cytotoxicity and blockade of growth factors (insulin-like growth factors (IGF) I and II) have been investigated. It is interesting to note that these factors (IGF I and II) are implicated in preneoplastic lesions induced by tamoxifen. Data published by Emons and colleagues [30] suggest that LH-RH analogues interfere with the signal transduction of growth factor receptors and related oncogene products associated with tyrosine kinase activity. They suggest that LH-RH agonists block the epidermal growth factor (EGF)-induced mitogen activated protein (MAP)-kinase activity of endometrial cancer cells.

Furthermore, the anti-angiogenic properties of LH-RH agonists [29] might contribute to their direct antiproliferative action and probably play a role in proliferative and preneoplastic lesions, such as those induced by tamoxifen.

The gynaecological follow-up could be much simpler and less extensive than the follow-up required while on tamoxifen alone. We know that the risk of endometrial cancer induced by tamoxifen is low [34–36] but, in patients with previous breast cancer, this potential risk leads to anxiety and so gynaecological examinations, echography and hysteroscopy are often repeated [37–40].

The question of the gynaecological follow-up of patients on tamoxifen is still a subject of controversy and debate in the literature. The guidelines uniformly recommend surveillance of symptomatic breast carcinoma patients; however, the American College of Obstetricians and Gynecologists (ACOG) and the National Cancer Institute (NCI) guidelines leave recommendations for endometrial surveillance of asymptomatic tamoxifen-treated breast carcinoma patients to the discretion of the provider.

According to Von Minckwitz [41], Barakat and the National Institutes of Health (NIH) 2000 (consensus), tamoxifen does not cause endometrial carcinoma, but increases the risk; tamoxifen-associated endometrial cancers seem to have a similar stage, grade and histology as endometrial cancers occurring in the general population. The authors believe that their prognosis is generally good and early detection would probably not improve outcomes significantly, but the cost of screening could be prohibitively high.

It was recently reported that the association between breast carcinoma, its treatment with tamoxifen and uterine sarcoma might be stronger than previously thought and that the latency period between starting tamoxifen and developing sarcoma could be longer (8.8 years) [42].

The importance of clinicians being alert to such diagnoses should be emphasised and the need for longer

surveillance programmes highlighted, even if patients are asymptomatic.

Another problem is the definition and choice of the best test to identify endometrial pathology and detect endometrial carcinoma in breast carcinoma survivors on tamoxifen [43]. Transvaginal sonography may provide a non-invasive and cheap means of screening the endometrium, but there is a high percentage of false-negative cases [43].

Our study strongly suggests that in patients receiving LH-RH agonists and tamoxifen, the follow-up may be safely limited to a pretreatment evaluation, follow-up and further examination only in cases of abnormal symptoms.

The most serious side effect of LH-RH agonists is the risk of bone loss. It is known that 6 months of therapy is associated with a substantial decrease of up to 8.2% in bone density, a phenomenon that, according to Devogelaer and Donnez [40], may not be entirely reversible 6 months after discontinuation of therapy. In our study, bone data showing the absence of statistically significant bone loss are very exciting findings. These results must be borne in mind when making future choices regarding the optimal endocrine combination to be administered, goserelin + tamoxifen or goserelin + aromatase inhibitors, because the preliminary results of the second association in metastatic studies demonstrate significant bone loss. This second association requires the addition of bisphosphonates to diminish the incidence of bone loss, but the economic impact of this supplementary measure is not negligible. Other objective side effects, essentially hot flushes, vaginal dryness and weight gain, must also be taken into account when making the choice of the ideal combination.

Although data upon which this study was based are incomplete, because we do not yet have bone data on patients who will have completed 5 years of therapy by the end of 2003, interesting conclusions can be drawn concerning the gynaecological and bone safety profile of the combination of goserelin and tamoxifen. Other questions remain unanswered: how long should ovarian ablation be implemented? Is 2, 3 or 5 years of goserelin equivalent to permanent ovarian ablation? [8]. This study strongly suggests that the association of LH-RH agonists and tamoxifen offers excellent protection against the endometrial side effects induced by tamoxifen. Moreover, tamoxifen appears to be able to diminish the significant bone loss induced by LH-RH agonists in young women.

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