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Clinical report

Goserelin as ovarian protection in the adjuvant treatment of premenopausal breast cancer: a phase II pilot study

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The aim of the present trial was to investigate the protective effects on ovarian function, and the efficacy and tolerability of goserelin added to adjuvant chemotherapy for early breast cancer. Following surgical treatment, 64 premenopausal patients with early breast cancer received goserelin 3.6 mg (every 28 days for 1 year) and an adjuvant treatment which was chosen according to the patient's prognosis. Median age was 42 years (range 27–50). ECOG performance status was 0–1 in all patients. Twenty-eight patients (44%) had estrogen receptor (ER)+ tumors and 36 (56%) patients had ER– tumors. Fifty-two (81%) patients had stage II disease and 12 (19%) had stage III disease. Eighteen patients received cyclophosphamide, methotrexate and 5-fluorouracil chemotherapy, 46 patients received an anthracycline-based regimen, and nine of them received high-dose chemotherapy and autologous peripheral blood progenitor cell transplantation. Fifty-one patients (80%) were irradiated. ER+ patients also received tamoxifen for 5 years. Serum estradiol was suppressed to values below 40 pg/ml in all patients. After a median follow-up of 55 months, 86% of patients had resumed normal menses, 84% of patients were disease-free and 94% were alive. The 1-, 3- and 5-year projected recurrence-free survival rates were 100, 81 and 75%, respectively. Five years after treatment one patient had a pregnancy that ended with a normal childbirth. No unexpected adverse events were reported. These data show that the addition of goserelin to adjuvant therapy of premenopausal patients with early breast cancer is well tolerated and protects long-term ovarian function. [© 2002 Lippincott Williams & Wilkins.]

Key words: Adjuvant chemotherapy, adjuvant hormone therapy, goserelin, high-risk early breast cancer.

Introduction

Adjuvant treatments improve the prognosis of premenopausal patients with breast cancer by clearing micrometastatic deposits present at the time of surgery. In particular, in premenopausal breast cancer patients, adjuvant chemotherapy improves absolute survival at 10 years by approximately 10%.[1] Similarly, after mastectomy, radiotherapy combined with adjuvant chemotherapy reduces loco-regional recurrences and prolongs survival in high-risk premenopausal women with breast cancer compared with chemotherapy alone.[2]

The efficacy of adjuvant chemotherapy in premenopausal patients has been attributed, in part, to drug-induced amenorrhea.[3] Indeed, the IBCSG Trial VI demonstrated that adjuvant chemotherapy in premenopausal women has a 2-fold effect, with both cytotoxic and hormonal components.[4] However, the ability of adjuvant chemotherapy alone to induce amenorrhea is variable, depending on both the regimen and the age of the patient. The average percentage of chemotherapy-related amenorrhea after cyclophosphamide (CTX), methotrexate (MTX) and 5-fluorouracil (5-FU) (CMF), given for at least 3 months, is 76% (range 49–100%) for women aged 40 years and over, but only 40% (range 21–71%) in women under 40.[5]

The additional benefit of achieving amenorrhea is also indicated by the fact that, after locoregional treatment, menopause induced by radiation significantly increases survival rate at 10 years when combined with low-dose prednisone compared with no further treatment.[6]

Hormonal adjuvant treatment is also extensively used for estrogen receptor (ER)+ early breast cancer and hormonal agents act by blocking the stimulatory effect of estrogen on the tumor cells. In particular, the antiestrogen tamoxifen is well established in the

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adjuvant treatment of early breast cancer, and reduces both mortality and recurrence in premenopausal patients with ER+ tumors.[7] In premenopausal women, the medical equivalent of oophorectomy can be achieved using luteinizing hormone-releasing hormone (LHRH) analogs, which decrease follicle-stimulating hormone (FSH) secretion as well as circulating levels of sex hormones.[8] These agents therefore prevent the production of estrogen. However, the beneficial effects of LHRH analogs may be explained not only on the basis of the decreased FSH secretion, but also by the antiproliferative effects, which have been shown *in vitro*.[9,10] Suppressing ovarian function with LHRH analogs has the added advantage of protecting the ovaries from damage by chemotherapy,[11,12] thus allowing the resumption of normal ovarian activity following cessation of treatment. Furthermore, non-menstruating women tolerate standard-dose and high-dose chemotherapy with peripheral blood progenitor cell (PBPC) transplantation better than those who are menstruating.

Given the potential benefits of estrogen suppression, the aim of present phase II pilot trial was to evaluate the protective effect of the LHRH analog goserelin on the ovaries during adjuvant treatment of early breast cancer, and the efficacy and tolerability of this combination.

Patients and methods

Study design and patient selection

Between September 1993 and May 2000, 64 consecutive patients who had been diagnosed with unilateral adenocarcinoma of the breast, stage PT2–3a, N−/+, M0 and who had undergone modified radical mastectomy or breast conserving surgery plus full axillary node dissection were recruited. Patients had to be actively menstruating, $\geqslant 18$ and $\leqslant 50$ years of age (premenopausal status with FSH < 10 mIU/ml), with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Macroscopic metastatic spread of the disease was excluded by usual criteria. The following laboratory parameters were required: granulocyte count $\geqslant 2000/\mu$l, platelet count $\geqslant 100\,000/\mu$l, hematocrit $\geqslant 30\%$, total bilirubin and AST levels $\leqslant 1.5 \times$ the upper limit of normal, serum creatinine concentration $\leqslant 1.8$ mg/dl, and left ventricular ejection fraction $\geqslant 50\%$. Bilateral bone marrow aspirates and biopsies were performed routinely in patients with > 5 positive axillary nodes and in the presence of radiographic or scintigraphic pelvic bone abnormalities. Patients with histologically documented metastases were excluded, as were those with malignancies other than curatively treated skin and cervical cancer. No prior chemotherapy or hormonotherapy were permitted.

Patients underwent clinical follow-up examinations every 6 months. The study was performed according to the Declaration of Helsinki, following local Ethics Committee approval. Written informed consent was obtained by all patients.

Date of relapse was defined as the time when recurrent disease was diagnosed. Disease-free survival (DFS) was defined as the length of time from the date of first chemotherapy to any relapse, the appearance of a second primary cancer or death, whichever occurred first. DFS and overall survival were estimated by means of the Kaplan and Meier product-limit method.[13] Adverse events were monitored using standard WHO criteria.[14]

Treatment plan

Patients received goserelin (Zoladex) 3.6 mg. s.c. 3 weeks after surgery and then every 28 days for 1 year. In addition, patients received adjuvant chemotherapy, the appropriate regimen being determined according to the characteristic of the tumor and to the prognosis of the patient (Figure 1).

Eighteen patients (27%) with T2–3 tumors, no axillary node, estrogen- and progesterone-positive receptors (ER+, PGR+) and low proliferative rate (evaluated by Ki-67)[15] were treated with 6 courses of CTX 600 mg/m^2, 5-FU 600 mg/m^2 and MTX 40 mg/m^2 day 1 and 8 (CMF), repeated every 4 weeks.

Eleven patients (17%) with T1–3 tumors, < 3 positive axillary nodes, ER− and PGR−, were treated with CTX 600 mg/m^2, epirubicin (EPI) 75 mg/m^2 day 1, and 5-FU 600 mg/m^2 day 1 and 8 (FEC) every 3 weeks for 6 courses.

Twenty-six patients (39%) with the same characteristics as the previous group and < 5 axillary nodes and two patients with > 10 axillary nodes who refused high-dose chemotherapy with PBPC transplantation, were treated with 4 courses of EPI 120 mg/m^2 and 8 courses of CMF every 3 weeks.[16]

Nine patients (14%) with > 10 axillary positive nodes received the first course of chemotherapy with EPI 120 mg/m^2. Granulocyte colony stimulating factor (5 μg/kg) was administered after chemotherapy for 9–10 days. Leukapheresis was performed and a median number of 8.45×10^6 CD34$^+$ cells were collected from each patient. These patients received 3 further courses of EPI 120 mg/m^2. High-dose chemotherapy consisted

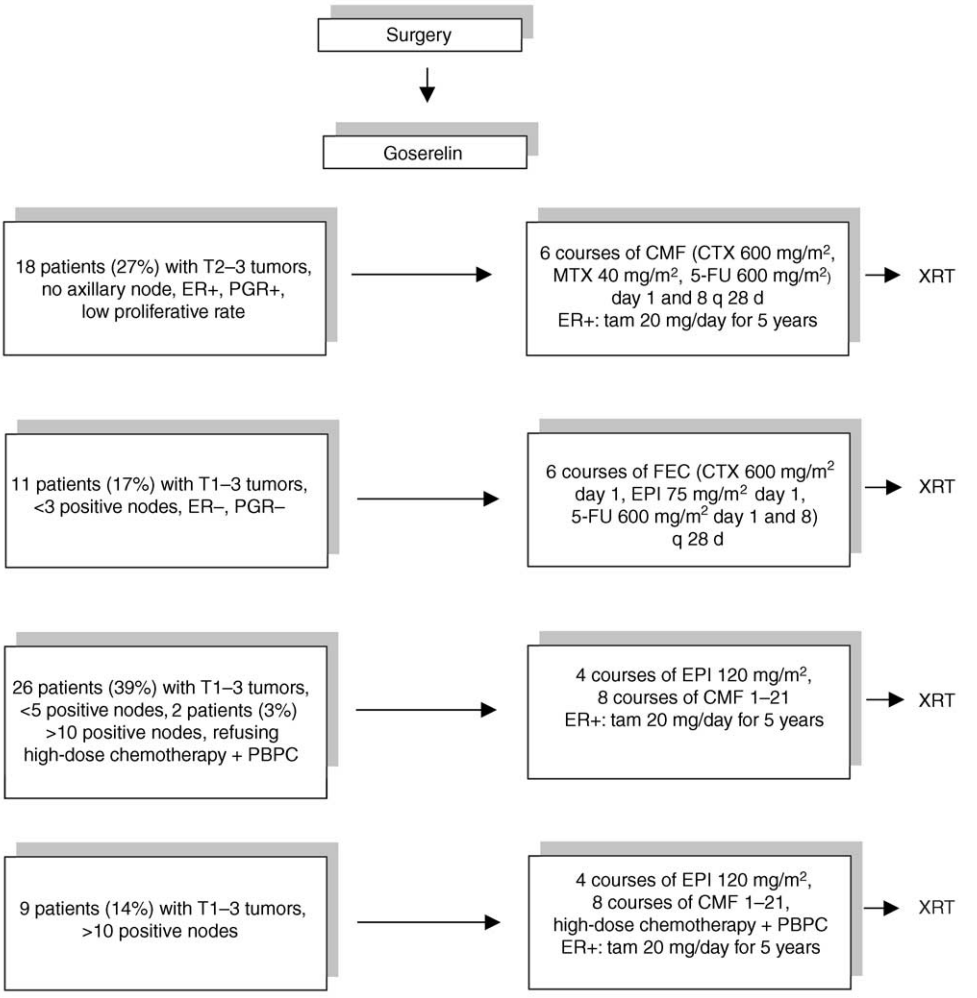

Figure 1. Treatment plan. XRT=radiotherapy.

of carboplatin 600 mg/m^2 days −3, −2, EPI 450 mg/m^2 days −3, −2 and melphalan 100 mg/m^2 day −1. PBPC were reinfused on day 0. After PBPC transplantation patients received 8 courses of CMF chemotherapy along with radiotherapy.

Forty-four patients that had been treated with segmental mastectomy and seven patients at high-risk of loco-regional relapse received radiotherapy that was started after the completion of the fourth course of chemotherapy. Following completion of chemotherapy, all patients with ER+ tumors received tamoxifen 20 mg daily for 5 years. The baseline demographics and tumor characteristics of patients are shown in Table 1.

Results

After a median follow-up of 55 months (minimum follow-up is 19 months) all patients had completed chemotherapy and the treatment with goserelin. When treatment was discontinued, a total of 55 women (86%) started regular menstruation, with appropriate hormone levels (all women <40 years), including five women treated with high-dose chemotherapy and peripheral progenitor cell transplantation. One patient completed a normal pregnancy 5 years after chemotherapy and radiotherapy, which resulted in the birth of a healthy child at term, and one patient had a voluntary abortion.

Disease recurred in 10 patients between 12 and 56 months after the start of treatment (Figure 2). Of these patients, six had loco-regional recurrence in the irradiated breast and one patient developed contralateral breast cancer. These patients were salvaged with modified radical mastectomy, and remain disease-free after a median of 54.2 months follow up. A further four patients had systemic recurrences, with a median time to progression of 24.3 months and a median survival time of 43.6

months. Of these, one patient (37 years) with ER– breast cancer and one positive axillary node at study entry developed a recurrence in the pelvic bones 3 years after the completion of the adjuvant treatment. She had a response to a Taxane-based chemotherapy and survived 29 months. A second patient, with 21 positive nodes and an ER– tumor had bone recurrence 25 months after initial chemotherapy. She was treated with radiotherapy, taxanes and gemcitabine chemotherapy but died 30 months after recurrence. The third patient with 17 positive axillary nodes and ER– breast cancer developed bilateral lung metastases after 12 months from the end of adjuvant chemotherapy. She was treated with a taxane-based chemotherapy regimen and had lung metastasectomy. This patient died 19 months after the recurrence. The last patient with ER– tumor and 10 axillary nodes who refused high-dose chemotherapy developed liver metastases within 23 months after operation and died 9 months after recurrence.

Table 1. Patient and tumor characteristics

Characteristics	No. of patients (%)
No. of patients	64 (100)
Age (years)	
median	42.5
range	27–50
Hormone receptor status	
ER+	28 (44)
ER−	36 (56)
Tumor histology	
ductal infiltrating	48 (75)
lobular infiltrating	5 (7.8)
medullary	5 (7.8)
other	6 (9.4)
Grading	
G2	24 (37.5)
G3	40 (62.5)
Clinical stage	
II	52 (81)
III	12 (19)
Nodes	
0	21 (32.8)
1	20 (31)
2–3	8 (12.5)
4–5	4 (6)
>5	11 (17.2)
Type of primary surgery	
mastectomy	20 (31)
quadrantectomy	44 (69)

The actuarial median overall survival rate (Figure 3) has not been reached yet, as 60 patients (94%) were alive when the analysis of the data was performed (December 2001). Projected DFS rates at 1, 3 and 5 years were 100, 82 and 75%, respectively. The projected overall survival rate at 5 years was 91%.

Tolerability

Adverse events reported during the chemotherapeutic treatment are shown in Table 2.

Goserelin. Thirteen patients (20%) complained of hot flushes. Serum estradiol was suppressed to values below 40 pg/ml in all patients.

CMF chemotherapy. No unexpected toxicity occurred during the administration of CMF chemotherapy and

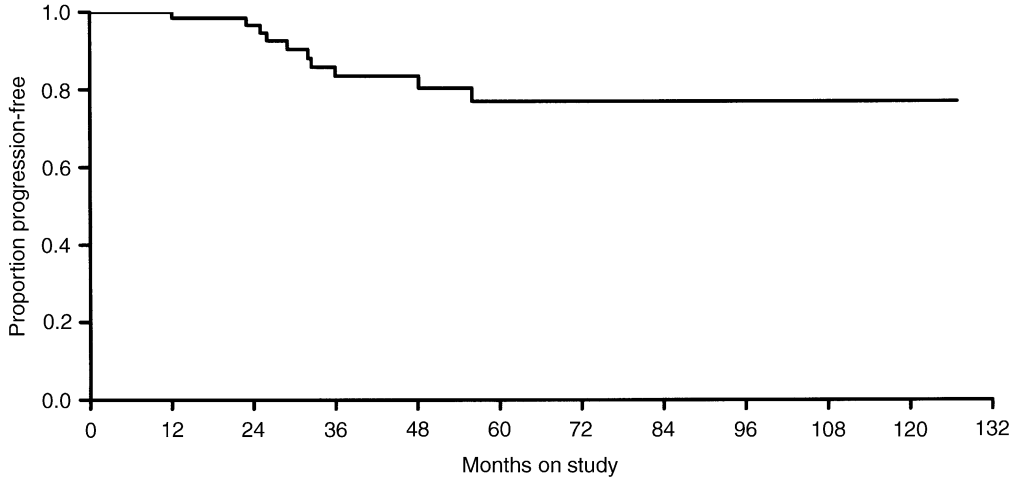

Figure 2. Time to progression. Events: 10 (15.6%). Censored: 54 (84.4%). Median time to progression: not reached after a median follow-up of 55 months.

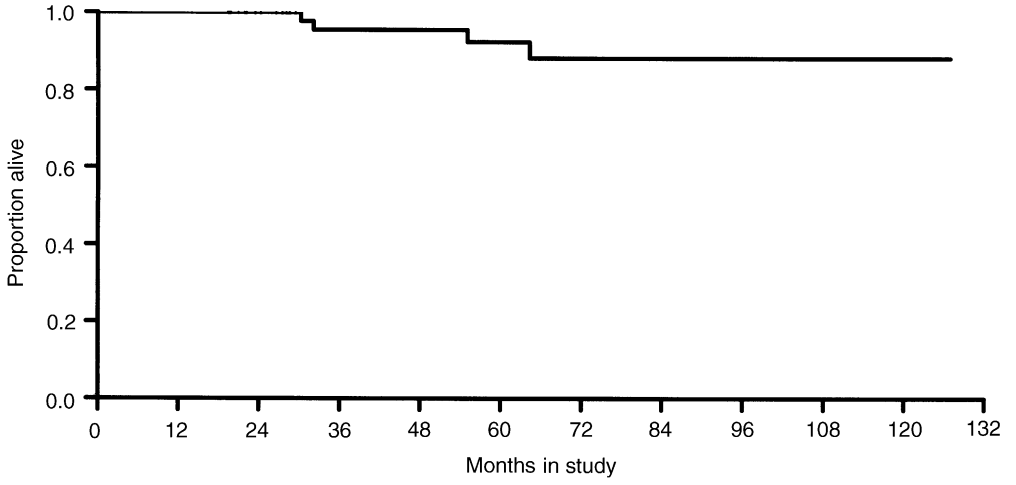

Figure 3. Overall survival. Events: 4 (6.2%). Censored: 60 (93.8%). Median survival not reached after a median follow-up of 55 months.

Table 2. Toxicity of chemotherapy

	CMF (18 patients) [*N* (%)]	Anthracycline-based chemotherapy (37 patients) [*N* (%)]	High-dose chemotherapy (9 patients) [*N* (%)]
Hematologic			
leukopenia (grade 3–4)	2 (11)	12 (32)	9 (100)
thrombocytopenia	0	3 (8)	9 (100)
anemia	0	0	3 (33)
Gastrointestinal			
nausea–vomiting (grade 2–3)	3 (17)	6 (16)	2 (22)
diarrhea (grade 2–3)	2 (11)	8 (22)	1 (11)
mucositis (grade 2–3)	0	8 (22)	3 (33)
Infection	0	1 (3)	1 (11)
Neurotoxicity	0	0	0
Alopecia	0	37 (100)	9 (100)

all 18 patients completed the scheduled treatment. Hematological toxicity grade 3 occurred in two (11%) patients. Grade 2 diarrhea occurred in two patients (11%), while three patients (17%) reported nausea and vomiting. There were no treatment-related deaths.

Anthracycline-based chemotherapy. Hematological toxicity grade 3–4 occurred in 12 of the 34 patients (32%) who were treated with anthracycline-based chemotherapy. Gastrointestinal toxicity (diarrhea and mucositis) was observed in eight patients (22%). Severe nausea and vomiting occurred in six patients (16%). Infection was reported in one patient. Grade 3 alopecia was observed in all patients. No significant reduction in left ventricular ejection fraction was observed in any patient and there were no treatment-related deaths.

High-dose chemotherapy. Nausea and vomiting occurred in two (22%) patients but were mild due to the appropriate use of ondansetron and dexamethasone. Neutropenia and thrombocytopenia grade 4 were observed in all patients. An absolute neutrophil count below 5×10^3/ml was observed for a median of 4.5 days (range 3–5 days), while a platelet count below 20×10^3/ml occurred for a median of 1 day (range 0–3 days). Three patients required a platelet transfusion (median 2 units). Anemia, which was infrequent due to the use of erythropoietin, occurred in three patients (33%). Three patients had fever above 38°C for a median

number of 3 days (range 0–6). Mucositis grade 2 occurred in three patients, while grade 3 diarrhea occurred in one patient (11%). One patient had a documented infection with a positive blood culture for *Staphylococcus epidermidis*. Bone pain was reported by two patients, with a median duration of 2 days. There were no treatment-related deaths.

Discussion

Breast cancer is a heterogeneous disease and to obtain the maximum benefit with the least toxicity, treatment has to be tailored to the clinical situation. Adjuvant chemotherapy improves both DFS and overall survival of premenopausal breast cancer patients.[1] Chemotherapy may be beneficial even in patients with no axillary node involvement with ER– tumors.[17] In fact, these patients will have distant metastases in approximately 30% of instances.[18] Endocrine therapies are firmly established in the management of all stages of breast cancer[19] and while in advanced disease they only prolong survival, they can be curative in the early phases.

In an analytical overview by the Early Breast Cancer Trialists' Collaborative Group, ovarian ablation was found to reduce the annual odds of recurrence and death by 20% for women aged less than 50 years affected by breast cancer and treated with ovarian ablation or chemotherapy.[19] The value of ovarian ablation in combination with tamoxifen was shown in a study of 709 premenopausal oriental women with operable breast cancer. Patients were randomized to oophorectomy plus tamoxifen for 5 years or observation only. After a median follow-up of 3.1 years DFS rates were 73 and 54%, in the adjuvant and observation groups, respectively (p=0.001). Corresponding overall survival rates were 76 and 65%. This trial, which was justified in a society that is deficient of medical resources, demonstrated, without confounding factors, the value of adjuvant ovarian ablation in premenopausal breast cancer patients.[20] The value of ovarian ablation appears to be independent of the method used. Thus, inhibition of ovarian function either using LHRH analogs or by surgical ovariectomy has been shown to be equally effective in the treatment of premenopausal patients with ER+ metastatic breast cancer.[21] In addition, several large randomized trials have recently confirmed the role of LHRH analogs in the adjuvant treatment of early breast cancer either as monotherapy[21] or in combination with tamoxifen and/or chemotherapy.[22–25]

In our trial, ovarian function was suppressed for 1 year using the LHRH analog goserelin. During this period, any cell surviving chemotherapy should have gone into programmed cell death (apoptosis) due to the absence of estrogen-stimulated cell growth.[26] Although chemotherapy is capable of eradicating sensitive, actively proliferating cell clones, disease may relapse if chemotherapy-resistant, slowly proliferating cells persist. Recently, it has been shown that the function of the LHRH analogs is not restricted to hormone deprivation. In fact, they behave like negative growth factors capable of regulating breast cancer cell growth, in particular antagonizing the action of minimal quantities of estrogen.[10] Both the estrogen deprivation caused by the LHRH analogs and their direct effect may induce apoptosis in cells that survive chemotherapy.[27]

LHRH analogs have previously been shown to prevent permanent amenorrhea associated with chemotherapy in premenopausal breast cancer patients wanting to maintain menstrual function and fertility.[28] All 13 patients in this study, whose age ranged between 26 and 39 years, resumed normal ovarian function after a mean of 4.9 months from completion of chemotherapy. Similarly, in the present study, 86% of patients started menstruating after completion of the treatment and one patient completed a pregnancy with full-term, healthy offspring.

Several studies have described that a subsequent pregnancy after breast cancer has no adverse effect on the prognosis.[29] This, indeed, may contribute to the psychological well being of the young woman with breast cancer. Ovarian failure, anyway, is the most significant long-term sequela of adjuvant chemotherapy in premenopausal breast cancer survivors.[5] In fact, premature menopause is associated with a wide variety of problems, including vasomotor (hot flashes and night sweats), psychological (mood sweep and disrupted sleep), genitourinary (atrophic vaginitis, dysuria), cardiovascular disease and infertility.[30] Moreover, rapid bone loss has been observed in 71% of premenopausal breast cancer patients that had a median age of 42 years, undergoing adjuvant chemotherapy for early-stage breast cancer.[31] In a series of 227 breast cancer patients, with a median age of 31 years, treated with a doxorubicin-based chemotherapy, 59% continued to menstruate after chemotherapy and 11% became pregnant.[32]

In our trial, ovarian suppression was combined with other treatments (chemotherapy, hormonal therapy and radiotherapy), because it has been demonstrated that combination therapy may be more effective. Regular menses, with appropriate hormone levels, returned in 86% of our patients who had a median age of 42.5 years.

In conclusion, from our data it appears that the administration of goserelin in combination with chemotherapy is feasible and well tolerated. Furthermore, it may offer benefit directly to women with ER+ breast cancer through hormonal deprivation and indirectly to all breast cancer patients by allowing normal menses to be restored upon the cessation of treatment.

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