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A. Sverrisdottir, M. Nystedt, H. Johansson, T. Fornander. Adjuvant goserelin and ovarian preservation in chemotherapy treated patients with early breast cancer: results from a randomized trial. *Breast Cancer Research and Treatment*, 2009, 117 (3), pp.561-567. 10.1007/s10549-009-0313-5 . hal-00535334

HAL Id: hal-00535334

<https://hal.science/hal-00535334>

Submitted on 11 Nov 2010

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Adjuvant goserelin and ovarian preservation in chemotherapy treated patients with early breast cancer: results from a randomized trial

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Received: 27 October 2008 / Accepted: 6 January 2009 / Published online: 20 January 2009
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Abstract The purpose of this randomized study was to examine if goserelin concomitant to CMF-chemotherapy as adjuvant treatment for premenopausal breast cancer, protects the ovaries from premature failure. A total of 285 premenopausal breast cancer patients, in a randomized adjuvant trial (Zoladex in premenopausal patients (ZIPP)), were assigned to a study on ovarian function. Node positive patients were assigned to CMF-(cyclophosphamide, methotrexate and 5-fluorouracil) chemotherapy in addition to endocrine therapy. All patients were randomly assigned to receive 2 years of goserelin, goserelin plus tamoxifen, tamoxifen alone or no endocrine treatment. We studied, if menses were affected in the treatment groups, up to 36 months after randomization. One year after completed CMF- and endocrine therapy, 36% of the women in the goserelin group reported menses, compared to 7% in the goserelin plus tamoxifen group, 13% in the tamoxifen group and 10% of the controls. Among women treated with goserelin, there was a statistically significant increase in the proportion of menstruating women, 1 year after completed treatment compared to at 24 months of treatment ($P = 0.006$), in contrast to all other treatment groups, who were unchanged or more often amenorrheic. In our study, there is some evidence of protective effect of goserelin on ovarian function in CMF treated women. This effect was not observed in the combined tamoxifen and goserelin treatment.

Keywords Breast cancer · Amenorrhea · Goserelin · Tamoxifen · Chemotherapy

Introduction

Premature ovarian failure (POF) and infertility is a frequent long-term result of cytotoxic chemotherapy, in young women with breast cancer [1–3]. The risk of ovarian failure is highly correlated to the woman's age, type of drug, dosage and duration [1, 4, 5]. In most studies, the majority of women over 40 years of age become amenorrheic after chemotherapy and the chances of restoring their ovarian function are meagre [6].

Approximately 25% of the women with breast cancer are premenopausal at the time of diagnosis [7]. As the incidence of breast cancer is rising, the number of young women diagnosed with the disease is increasing [8]. Lately, it has become more common for women to delay family building and childbirth, and it is not unusual for women over the age of 40 to consider pregnancy. To avoid signs and symptoms of early menopause is an even more frequently reported request of this group of patients. Pregnancies after breast cancer do not adversely affect the prognosis [9, 10] and should in general not be discouraged. Young age at diagnosis appears to be an independent risk factor for recurrence or metastatic disease [11] and young patients' tumours tend to be more aggressive. Therefore, adjuvant cytotoxic chemotherapy is often recommended for this group of patients. Earlier studies have shown higher rates of amenorrhea from CMF compared to anthracycline-based therapy, but the additional effect of anthracyclines or taxanes in comparable duration, dose-dense or dose-intense schemes is not clear [12–15].

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Treatment induced ovarian ablation, whether by endocrine- or chemotherapy, radiation or surgery, results in increased disease free survival and overall survival in premenopausal endocrine responsive breast cancer [16]. However, it is not clear whether permanent ovarian failure is superior to temporary amenorrhea. There have also been concerns that combined chemo-endocrine treatment might be inferior to sequential treatment [17]. The additional effect of ovarian ablative treatment after chemotherapy has as well been debated and is currently under investigation in several international trials such as the Suppression of Ovarian Function trial (SOFT). So far, recent results from a meta-analysis of randomized luteinizing hormone release hormone agonist (LHRH-a) trials show that combined therapy is not inferior and there is an additive effect from LHRH-a after chemotherapy, at least for women younger than 40 years [18].

Besides infertility, POF has multiple physiologic consequences affecting many organs and increases the risk of other long-term side effects, such as osteoporosis, vasomotor symptoms, cardiovascular disease and sexual dysfunction [2, 3, 12, 19–21]. As treatment results improve and more women have excellent prognosis after adjuvant chemotherapy, the demands for information on adverse effects increases and greater effort is needed in attempt to assure physical and psychological well being after treatment. Treatment induced infertility among women desiring children, can account for great psychological stress and should be prevented if possible [22]. Although “prophylactic” fertility treatment by cryopreservation of fertilized ova or ovarian tissue can be offered to some of these patients, such approach is not feasible for all, due to factors such as cancer treatment delay and cost. These approaches are still very experimental and do not restore hormone production for a longer duration. Ovarian protection by endocrine manoeuvring could therefore render an important therapeutic option in prevention of POF, in young women with malignant disease, where adjuvant cytotoxic chemotherapy is recommended.

In the literature, there are some reports on the protective effects from an LHRH-a use concomitant to chemotherapy [3, 23–26]. The mechanism behind such a protection is unknown, but may be explained by LHRH-a acting by suppression of the pituitary-gonadal axis, resulting in an inactive or resting state of the ovaries which might preserve primordial follicles from permanent cytotoxic damage. However, there is to our knowledge, no data from randomized studies of ovarian effects of LHRH-a in addition to chemotherapy and tamoxifen in breast cancer patients. The present study was designed as a sub-protocol to a randomized adjuvant trial (Zoladex In Premenopausal Patients (ZIPP)), to examine the effects of the LHRH-a goserelin on menstrual status, when used concomitant to CMF-chemotherapy, with or without tamoxifen.

Patients and methods

The ZIPP study was a collaboration of four randomized multi-center trials (Stockholm Breast Cancer Study Group, Sweden, SE Sweden Breast Cancer Group, Cancer Research UK and UCL Cancer Trials centre, UK and Gruppo Interdisciplinare Valutazione Interventi in Oncologia, Italy) and has been described elsewhere [27]. In the Stockholm centers, node positive women were allocated to adjuvant CMF chemotherapy (six cycles of cyclophosphamide 600 mg/m², methotrexate 40 mg/m² and 5-fluorouracil 600 mg/m² intravenously days 1 and 8, every 28 days), in addition to endocrine therapy. Patients operated on with breast conserving surgery received post-operative radiotherapy 50 Gy through 5 weeks, to the breast. Patients with four or more positive lymph nodes received additionally loco regional radiotherapy including the chest wall, axillary- and supraclavicular lymph nodes 46 Gy through 4.5 weeks. The dose of tamoxifen was 40 mg/day orally and goserelin 3.6 mg subcutaneously every 28 days. For goserelin, every injection was documented in the patient records. The treatment duration for both tamoxifen and goserelin was 2 years and was given irrespective of hormone receptor status, according to the inconclusive data at the time of study. Endocrine treatment was given concomitant to chemotherapy. The randomization was stratified in three groups: node negative patients receiving no chemotherapy, patients with 1–3 positive lymph nodes receiving chemotherapy, and patients with four or more positive lymph nodes receiving both chemotherapy and loco-regional radiotherapy (Fig. 1). Randomization was carried out by telephone to a central office where the patient identifiers were recorded before the allocated treatment was revealed to the responsible physician. Treatment allocation was based on balanced lists using the permuted block technique.

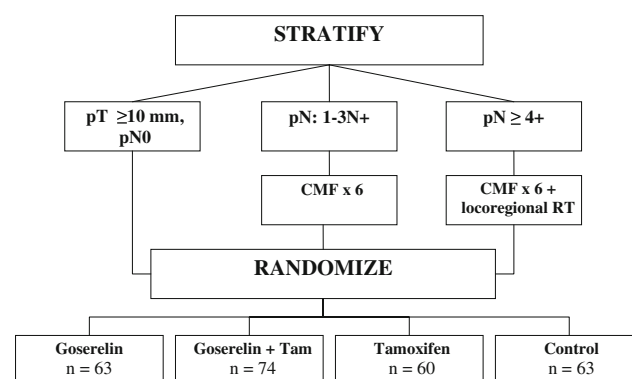


Fig. 1 Study design. All patients with breast conserving surgery were assigned radiotherapy (RT) to the breast, 50 Gy's in 5 weeks. Abbreviations: pT: pathological tumour size in millimetres, pN: pathological nodal status, CMF: cyclophosphamide, methotrexate and 5-fluorouracil. Tam: tamoxifen

Within the ZIPP-trial, the Stockholm Breast Cancer Study Group initiated sub-studies of treatment related side effects, such as effects on ovarian function, bone mineral density, return to work and quality of life. Between October 1990 and June 1994, 285 out of 408 (70%) eligible patients in the randomized trial were recruited to the study of ovarian function. Patients were allocated to the study before randomization to the treatment arms. The inclusion criteria were invasive breast cancer ≥ 10 mm, premenopausal menstrual status (defined as last menstruation < 6 months earlier), primary surgery consisting of a mastectomy or a sector resection plus axillary node dissection and no clinical evidence of distant metastases. The exclusion criteria were inoperable breast cancer, prior radiotherapy or neo-adjuvant chemotherapy and prior or concurrent endocrine therapy. Self-reporting questionnaires were obtained from patients at scheduled visits at the outpatient clinic at baseline (before randomization), 3 months, 12, 24, 30 and 36 months after randomization. The study was designed and conducted according to WHO's Good Clinical Practice guidelines and was approved by the Karolinska Institute Regional Ethics Committee.

Instrument

The questions regarding menses were a part of the questionnaire designed for the ZIPP sub-study of side effects as has been reported [20]. The women reported, either if menses had ceased, had not ceased but become scanty or not ceased, since prior survey and visit to the outpatient clinic. The first survey was made at the time of randomization and the time-period since prior survey, varied from 3 months up to 9 months.

Statistical methods

All analyses were performed according to the intention-to-treat principle. In the analyses for each time point, menses self reported as regular or irregular were assessed as having menstruations. Patients reporting absence of menses were assessed as amenorrheic. Patients with recurrent disease were excluded from the analysis. The analyses are presented as results at baseline, 3 months, 12, 24, 30 and 36 months. Fisher's exact test was used to assess differences between the treatment groups, as shown in "two by two tables".

Results

Baseline characteristics were well balanced as listed in Table 1. Recruitment of patients and distribution to different treatment arms is presented in Fig. 2.

A total of 285 (70%) out of 408 eligible patients were recruited for the study of ovarian function. The 123 patients not recruited, was due to patient's preference. Additionally twenty-five patients were excluded because of recurrent disease. The remaining 260 patients were included in the analyses. Self-reporting questionnaires were obtained from patients before randomization to endocrine treatment up to 36 months after randomization. Information on menstrual status was missing from four patients at baseline, twelve patients at 3 months and additionally 39 patients up to 36 months.

Tolerability study of this cohort has shown that treatment with goserelin and tamoxifen resulted in reversible menopausal symptoms whereas CMF treated experienced symptoms throughout the study period as has been reported [20].

Amenorrhea

CMF chemotherapy treated

At baseline, 6% (7/119) women reported absence of menses, which was in accordance to inclusion criteria, as premenopausal status was defined at last menses within less than 6 months. At 3 months, 50% (13/26) of the women in the control group reported amenorrhea. For women receiving tamoxifen (T), the figure was 73% (19/26). Women treated with goserelin (G) or goserelin plus tamoxifen (GT), reported amenorrhea in 93–94% (26/28 and 34/36 respectively) of cases. At 24 months, i.e. after 2 years of endocrine treatment, 85% (17/20) of the controls, 95% (19/20) of the T group, 97% (29/30) of the GT and 92% (22/24) of the G group were amenorrheic. At this time point, there was no statistically significant difference in amenorrhea for goserelin treated compared to all other treatment groups ($P = 1.00$) (Table 2). Six months after cessation of endocrine treatment, the proportion of amenorrheic women continued to increase to 94% (16/17) for the controls, was 87% (20/23) for the T group, unchanged 92% (24/26) for the GT group, but only 67% (14/21) of the women treated with goserelin reported absence of menses at this time point.

At 36 months, i.e. 1 year after stopped endocrine treatment, the proportion of amenorrheic women in the control group was 90% (18/20), 87% (20/23) for the T group, 93% (27/29) for the GT group but had decreased to 64% (14/22) for the G group. The proportion of menstruating women in the G group increased statistically significant, compared to all other groups where menses were unchanged or decreasing between 24 and 36 months ($P = 0.006$) (Table 2 and Fig. 3).

Table 1 Patient characteristics

Endocrine treatment	Goserelin <i>n</i> = 63	Goserelin + Tam <i>n</i> = 74	Tamoxifen <i>n</i> = 60	Control <i>n</i> = 63
CMF treated (%)	29 (46)	37 (50)	29 (48)	28 (44)
Age <45 years	10 (34)	12 (32)	10 (34)	11 (39)
Age ≥45 years	19 (66)	25 (68)	19 (66)	17 (61)
Age in years				
Median (range) all	45 (29–54)	45 (29–54)	45 (29–53)	46 (36–55)
CMF	45 (36–51)	46 (35–54)	45 (29–53)	45 (29–53)
Not CMF	46 (36–55)	45 (29–52)	45 (33–52)	45 (32–54)
Tumour size				
<20 mm	29	37	30	29
>20 mm	34	35	30	34
Unknown	0	2	0	0
Nodal status				
Positive	29	37	28	29
Negative	34	37	32	34
ER status				
Positive	45	45	45	46
Negative	12	21	9	11
Unknown	6	8	6	6
PgR status				
Positive	41	49	41	40
Negative	16	17	13	15
Unknown	6	8	6	8
Surgery				
Partial mastectomy	42	43	33	35
Mastectomy	21	31	27	28

Tam tamoxifen, *ER* estrogen receptor, *PgR* progesterone receptor, *CMF* cyclophosphamide, methotrexate and 5-fluorouracil, *n* number of patients

ER/PgR positivity was defined as a receptor content ≥0.05 fmole/g DNA

Not CMF treated

All randomized patients reported having menses at baseline.

At 3 months, 9% (3/34) of the controls, 21% (6/29) of the T group, 86% (31/36) of the GT group and 97% (32/33) of the G group were amenorrheic. At 2 years after randomization, 13% (4/31) of the controls, 21% (5/24) of the T-group, 69% (22/32) of GT-group and 82% (23/28) of the G-group reported amenorrhea. Six months after completed endocrine treatment, 17% (5/29) of the controls, 12% (3/24) of the T group, 28% (8/29) of the GT group and 37% (10/27) of the G group were amenorrheic. At 36 months, i.e. 1 year after completed endocrine treatment, 20% (6/30 and 5/25 respectively) of the controls and T group, 32% (10/31) of the GT group and 41% (12/29) of the G group were amenorrheic. At 36 months, i.e. 1 year after stopped endocrine therapy, there was no statistical significant difference in menstrual status of women treated with goserelin compared to all other treatment groups ($P = 0.15$) (Fig. 3).

Discussion

This was a randomized adjuvant study of LHRH-a effects on ovarian function in breast cancer patients treated with chemotherapy with or without concomitant tamoxifen. Our study shows that amenorrhea is significantly less frequent one year after completed treatment among patients treated with goserelin as the only additive endocrine therapy during chemotherapy. This suggests that goserelin has a role in protecting ovarian function in cytotoxic milieu as has been reported in several non-randomized studies [24–26, 28–33]. The size of this effect is nevertheless moderate and may be due to several effect modifiers in our study. In the present study, the age is rather high for a premenopausal population, with a mean of 45 years. This is an age where natural menopause approaches and age above 40 years is undisputedly a strong risk factor for permanent chemotherapy induced amenorrhea [34].

The timing of goserelin treatment is another factor, which possibly may not be optimal concerning a potential effect on preservation of ovarian function. Theoretically,

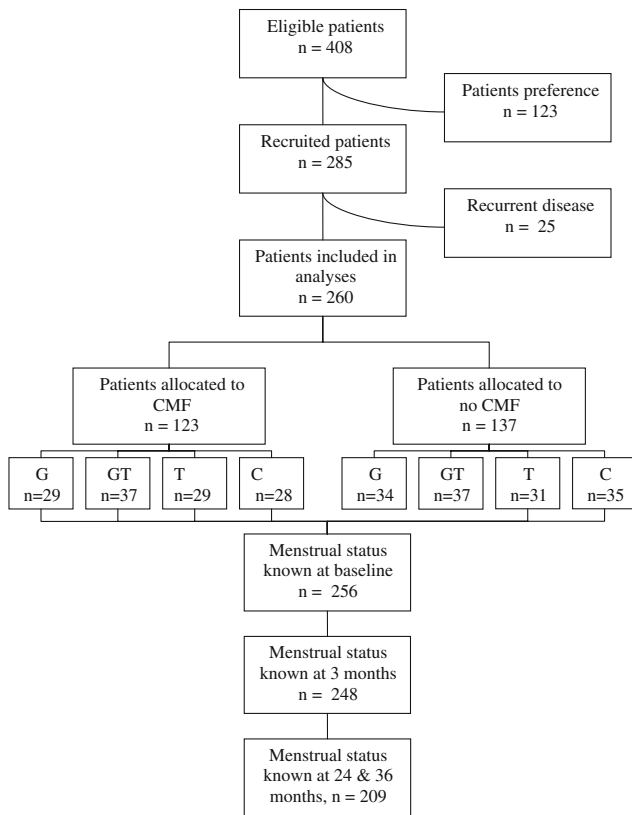


Fig. 2 Patients recruitment and compliance to study protocol. Abbreviations: CMF: cyclophosphamide, methotrexate, fluorouracil, G: goserelin, GT: goserelin plus tamoxifen, T: tamoxifen, C: control

LHRH-a treatment should preferably start at least 2 weeks before initiation of chemotherapy as an approach to optimise ovarian suppression in advance of cytotoxic chemotherapy effects. In our study, however, goserelin injections were started simultaneously as the first CMF course, which may be too late for achieving full effect.

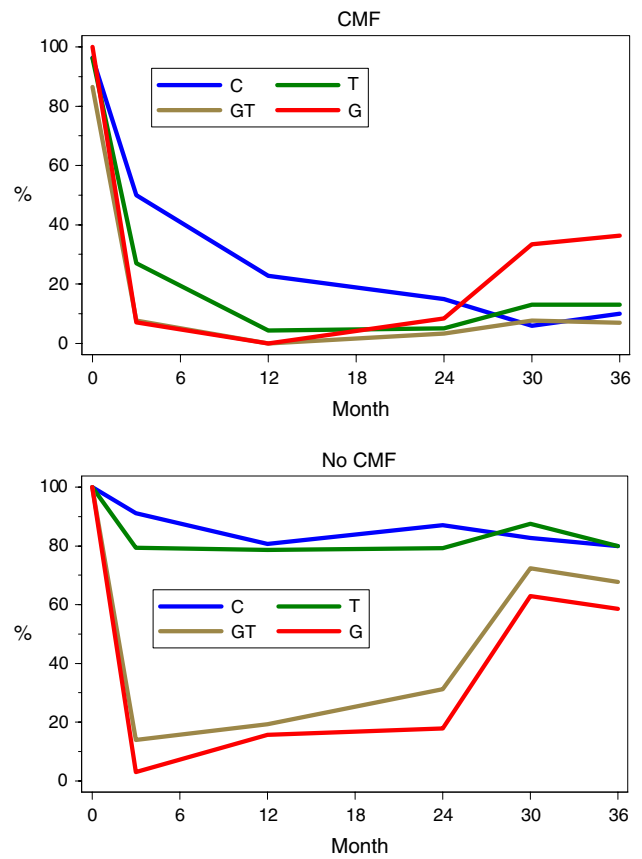


Fig. 3 Ovarian function according to treatment. Percentage of women menstruating at different time points. C: control, T: tamoxifen, GT: goserelin plus tamoxifen, G: goserelin

When tamoxifen was added to goserelin in CMF treated women, there was no statistical significant change in the proportion of menstruating women, 1 year after stopped treatment, in contrast to the CMF treated women receiving goserelin alone. The mechanism behind this is unclear but

Table 2 Menstrual status in CMF-chemotherapy treated women

Menses	G versus C		G versus T		G versus TG		G versus all other	
	G	C	G	T	G	TG	G	C, T or TG
<i>After 2 years of endocrine treatment</i>								
Yes	2 (8%)	3 (15%)	2 (8%)	1 (5)	2 (8%)	1 (3%)	2 (8%)	5 (7%)
No	22 (92%)	17 (85%)	22 (92%)	19 (95%)	22 (92%)	29 (97%)	22 (92%)	65 (93%)
Total	24	20	24	20	24	30	24	70
Fishers exact	$P = 0.65$		$P = 1.00$		$P = 0.58$		$P = 1.00$	
<i>One year after stopped endocrine treatment</i>								
Yes	8 (36%)	2 (10%)	8 (36%)	3 (13%)	8 (36%)	2 (7%)	8 (36%)	7 (10%)
No	14 (64%)	18 (90%)	14 (64%)	20 (87%)	14 (64%)	27 (93%)	14 (64%)	65 (90%)
Total	22	20	22	23	22	29	22	72
Fishers exact	$P = 0.071$		$P = 0.091$		$P = 0.013$		$P = 0.006$	

G goserelin, T tamoxifen, C control, GT goserelin plus tamoxifen

can be due to tamoxifen obscuring the goserelin effect possibly by its oestrogen agonistic properties.

The use of menstruations as a sole surrogate for ovarian function might be regarded as a limitation of our study whereas measurements of follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol and anti-Müllerian hormone have been reported by Anderson et al., to be a more precise assessment [35]. However, a previous study by Poikonen et al., showed that post-chemotherapy menstrual status is a clinically useful marker of menstrual status and FSH and LH less reliable [36]. The evaluation of serum markers such as FSH and LH after chemotherapy is therefore challenging and furthermore not appropriate during the period of goserelin treatment. Tamoxifen is as well reported to affect the gonadotrophins by decreasing FSH and LH levels [37, 38].

Possible confounders, such as the previous use of contraceptive pills as well as hormone replacement therapy, due to menopausal symptoms, were not examined, but are expected to be evenly distributed between treatment arms in a randomized study like this.

Our results are in accordance with several earlier studies where CMF frequently induces early and irreversible amenorrhea [1, 3, 12, 39]. CMF was standard chemotherapy at the time of the study, whereas anthracycline based chemotherapy, with or without taxanes, have recently become more commonly used. The extent of ovarian suppression from these agents is not well defined but seems nevertheless substantial [34]. Current trials investigating goserelin prophylaxis during taxane-based chemotherapy, such as the ZORO trial by the German Breast Group, may clarify this effect. A meta-analysis of randomized adjuvant trials has recently shown no therapeutic benefit with combination endocrine therapy versus tamoxifen or goserelin alone [18]. If these findings will be repeated in an ongoing and extended up-date of the ZIPP-trial, it may turn out that goserelin alone is equally as effective treatment as in combination with tamoxifen or tamoxifen alone except for the possibility of ovarian protection.

In conclusion, chemotherapy, ovarian ablation and tamoxifen improve survival in hormone receptor positive premenopausal breast cancer. The present study shows that the addition of LHRH-a goserelin alone may as well prevent permanent amenorrhea, for some women receiving cytotoxic chemotherapy. Young breast cancer patients should therefore not only receive adequate information on possible long-term risks of chemotherapy therapy but should as well be considered for the option of goserelin treatment when reversible amenorrhea is strongly desired. The results of this study must, however, be interpreted cautiously because of several limitations in design and data collection and need to be confirmed in future randomized trials before any change in clinical routine is justified.

Acknowledgements We thank nursing staff at the Breast cancer units, Department of Oncology, Karolinska Hospital for their excellent work coordinating patients' visits, tests and questionnaires. This study was supported by the Swedish Cancer Society.

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