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ORIGINAL ARTICLE

GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial

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Background: Chemotherapy-induced premature ovarian insufficiency (POI) impacts fertility and other aspects of women's health. The OPTION trial tested whether administration of a gonadotropin-releasing hormone agonist during chemotherapy for early breast cancer reduced the risk of POI.

Patients and methods: This was a prospective, randomized, parallel group study of the gonadotropin-releasing hormone agonist goserelin administered before and during chemotherapy for breast cancer with stage I–IIIB disease. The primary outcome was amenorrhoea between 12 and 24 months after randomization, supported by elevated follicle stimulating hormone concentrations to give an additional analysis as rate of POI.

Results: A total of 227 patients were randomized and the primary analysis was conducted on 202 patients. Goserelin reduced the prevalence of amenorrhoea between 12 and 24 months to 22% versus 38% in the control group ($P = 0.015$) and the prevalence of POI to 18.5% versus 34.8% in the control group ($P = 0.048$). Follicle stimulating hormone concentrations were also lower in all women treated with goserelin at both 12 and 24 months ($P = 0.027$, $P = 0.001$, respectively). The effect of goserelin was not statistically significant in women >40 years. Assessment of the ovarian reserve using anti-Müllerian hormone showed a marked fall in both groups during treatment to median values of 5% of pretreatment levels in the control group and 7% in the goserelin group, which were not significantly different between groups.

Conclusion: This study shows that goserelin reduced the risk of POI in women treated with chemotherapy for early breast cancer, with particular efficacy in women aged ≤40 years old. The degree of ovarian protection also seems limited and the clinical significance for fertility and longer term prevention of estrogen deficiency-related outcomes needs to be determined.

Key words: breast cancer, ovary, GnRH analogue, chemoprotection

Introduction

The improved survival of women with early breast cancer in recent years [1] has led to an increased interest in the long-term consequences of treatment. Amongst these, ovarian toxicity from chemotherapy is important in younger women, as it may result in loss of fertility and early menopause (premature ovarian insufficiency, POI) with consequent increased risk of a range of adverse health effects including menopausal symptoms, osteoporosis, sexual dysfunction, cardiovascular disease and loss of neurological function [2].

A number of observational studies have suggested a benefit from gonadotropin-releasing hormone (GnRH) agonist suppression of ovarian function, but the data from randomized controlled trials (RCTs) remain mixed [3–7]. The most recent substantial RCT in

women with breast cancer [8] found evidence of reduced risk of ovarian failure with goserelin treatment during chemotherapy, and meta-analyses also report varying results [9, 10]. Trials in women with Hodgkin lymphoma also report varying results [11, 12].

Recall of menses may be unreliable unless based on a daily diary, and while amenorrhoea is clear, infrequent or irregular menses may indicate incipient POI. This trial was set up to establish whether the use of goserelin in women who require chemotherapy for operable hormone-insensitive breast cancer or for whom ovarian suppression is not considered a necessary part of treatment, may reduce the risk of POI. This primary outcome was the prevalence of amenorrhoea at 12–24 months, secondarily combined with elevated follicle-stimulation hormone (FSH) concentration giving the prevalence of POI.

Anti-Müllerian hormone (AMH) is also a valid and valuable marker of ovarian follicle reserve [13]. Pre-treatment AMH has been suggested to predict long-term ovarian function following chemotherapy for early breast cancer, and post-treatment concentrations are an indicator of the remaining ovarian reserve in women who maintain menstrual function, thus providing a quantitative estimate of the degree of ovarian protection [14, 15].

Methods-Patients

Premenopausal patients with histologically confirmed breast cancer who were to receive adjuvant or neo-adjuvant chemotherapy were eligible for 'OPTION'. All patients gave informed consent and the study received Ethical Committee approval (South West Multicentre Research Ethics Committee, ref MREC/03/6/90). The original protocol restricted the entry of patients to those with ER-negative tumors only, but patients with ER-positive tumors for whom the investigator did not deem ovarian suppression necessary as part of the treatment were subsequently allowed entry to the trial after a protocol amendment. The breast cancers could be up to stage IIIB (T1-T4 with N0-2) and complete excision of the tumor before adjuvant chemotherapy or planned after neoadjuvant therapy was required. The patients had to be pre-menopausal (defined as regular menses in the 12 months prior to chemotherapy). Metastatic disease was an exclusion criterion. Patients who had had prior chemotherapy or endocrine therapy were ineligible. Chemotherapy regimens included six to eight cycles of cyclophosphamide and/or anthracycline-containing regimens with or without a taxane. Patients were randomized to receive a 3.6-mg goserelin implant or nothing starting at least 1 week, and preferably 2 weeks, prior to the start of the chemotherapy treatment, and continuing goserelin 3–4 weekly until the end of the chemotherapy treatment. Chemotherapy had to start within 8 weeks of definitive surgery. Radiotherapy was as per standard protocol for each centre.

Randomization was centrally performed by telephone to the trial center, eligibility was confirmed verbally, and treatment was allocated by computer-generated lists. Pre-treatment evaluation included history and physical examination, haematology and biochemistry profiles, chest X-ray, electrocardiograph, and measurements of estradiol, FSH, and luteinizing hormone (LH) which were performed locally; serum was also stored for later measurement of AMH which was performed centrally using the Roche Elecsys automated assay.

Patients were followed-up 6-monthly for 2 years and then 12-monthly for a further 3 years. Hormone levels were checked at cycle 3, after the final cycle, then at 9 months, 12 months, then annually. A menstruation diary was kept for 24 months from the start of chemotherapy.

Statistical analysis

The primary outcome was the rate of amenorrhea, i.e. no menses between 12 and 24 months after randomization, also combined with elevated FSH concentrations to give rate of POI. For the sample size calculation, it was assumed that the rate of amenorrhea would be 40% in the 40 years and under age-group and 80% in the over 40 age-group. At the time of conception of the trial, two uncontrolled studies had suggested that goserelin might reduce the rate of premature menopause to 20%. A one-sided test with 5% false-positive rate was used to calculate the sample size to give an 80% chance of detecting an absolute reduction from 40% to 20% in the 40 years and under group and from 80% to 55% in the older age group. It was intended to recruit a total of 250 patients and allowing for a 15% loss to follow-up. Randomization was stratified by age (aged 40 years or younger and those over 40 years) and by center.

Analysis of binary endpoints was conducted using a two-sided Fisher's Exact test. Comparisons of the hormone concentrations between treatment groups were by the Mann–Whitney test. An exploratory logistic regression analysis was performed to assess the predictive value of age, total cyclophosphamide dose and baseline AMH for amenorrhoea. To ensure an intention to treat analysis where the primary end-point data were unobtainable, two alternative imputations were made:

1. Best case: All patients with missing information were assumed not to have experienced amenorrhea (regardless of treatment arm).
2. Worst case: All patients with missing information were assumed to have experienced amenorrhea (regardless of treatment arm).

Results

About 227 patients were randomized between 26 August 2004 and the end of December 2009. Of these, three in each arm were omitted from this analysis because they had died within 24 months of randomization and had therefore unknown menstrual status at 24 months. The age distribution, chemotherapy regimens and ER status for these 221 patients are described in Table 1, and did not differ between the two groups. For a further 19 patients (11 in the control arm and 8 in the intervention arm), menstrual status during the interval between the 12-month follow-up visit and the 24-month follow-up visit could not be determined from the data available. The primary analysis was therefore conducted on 202 patients (Figure 1).

Primary outcome

The prevalence of amenorrhoea during chemotherapy was, as expected, much higher in the goserelin group (97.9% versus 63.5%, $P < 0.0001$). By 12 months, menses had resumed in many women, in both groups.

Table 1. Demographics of patients recruited to the study

	N	Chemotherapy alone 118	Chemotherapy plus goserelin 103
Age at randomisation (years)			
	N	118	103
	Median	38.8	37.9
	(Range)	(24.8, 51.1)	(25.9, 50.0)
	≤40 (%)	65 (55)	65 (63)
	>40 (%)	53 (45)	38 (37)
ER negative/positive (%)		66/52 (56/44)	60/43 (58/42)
Pretreatment AMH (ng/ml)	Mean (SEM)	1.10 (0.19)	1.47 (0.26)
Planned chemotherapy			
Anthracycline regimens without taxane (ACF)	*N* (%)	80 (68)	68 (66)
Anthracycline regimens with taxane (ACFT)	*N* (%)	38 (32)	35 (34)
Cumulative dose of cyclophosphamide, mg	Median (range)	5940 (1400–6930)	5940 (2970–5940)

Regimen abbreviations: A, anthracycline; C, cyclophosphamide; F, 5-fluorouracil; T, taxane.

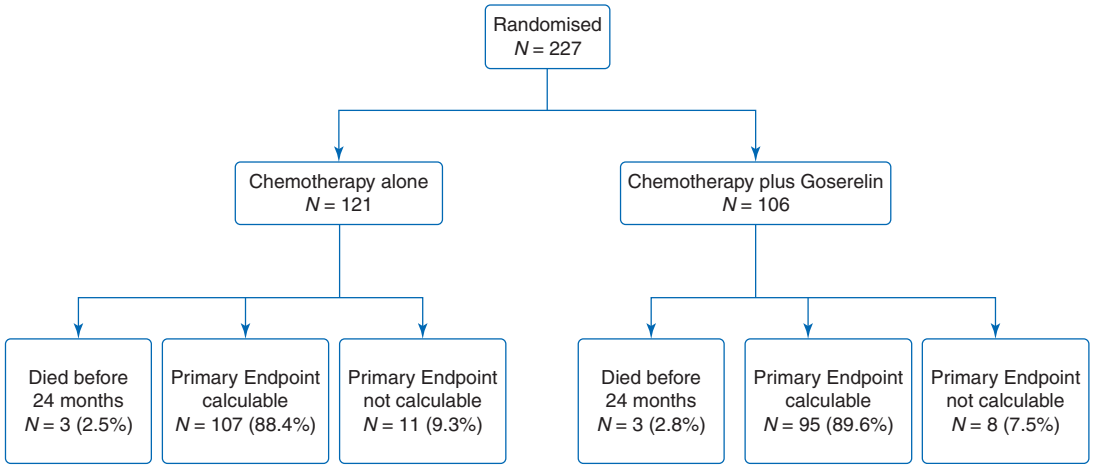

Figure 1. Consort diagram showing disposition of patients recruited.

The main outcome of this trial showed a difference in the prevalence of amenorrhoea between 12 and 24 months, being 22% in the goserelin group versus 38% in the control group ($P = 0.015$, Table 2). After imputing missing data both as worst case (all with amenorrhoea) or best case (none with amenorrhoea) scenarios, there remained significant differences between groups, with reduced prevalence of amenorrhoea in the goserelin group (Table 2). This apparent protective effect of goserelin was further assessed using the definition of POI, i.e. amenorrhoea with elevated FSH concentrations using a FSH cutoff of 25 IU/L [16]. The prevalence of POI in the goserelin group was 18.5% versus 34.8% in the control group ($P = 0.048$), thus closely mirroring the amenorrhoea results.

Given the likely importance of age in determining risk of chemotherapy-related amenorrhoea, groups were stratified by age, using a cutoff of 40 years. This analysis showed a protective effect of goserelin on both the prevalence of amenorrhoea alone and on POI (amenorrhoea plus high FSH) in women aged ≤40 (amenorrhoea: 10.0% versus 25.4%, $P = 0.032$; POI: 2.6% versus 20.0%, $P = 0.038$). The effect was less clear and not statistically significant in women >40 years (amenorrhoea: 42.9% versus 54.2%, $P = 0.376$; POI: 42.3% versus 47.2%, $P = 0.798$).

Nine pregnancies occurred in women in the goserelin group (including two pregnancies each for two women) and six in the control group (including two pregnancies in one woman). A total of 24 deaths occurred, 9 in the goserelin group and 15 in the control group.

Hormonal evaluations

The control group showed a fall in estradiol concentrations during and following chemotherapy, with resultant rises in FSH and LH (Figure 2). The goserelin group showed the expected significant reductions in LH, FSH and E2 during treatment (Figure 2), with the estradiol changes also reflecting the effect of chemotherapy. Consistent with the reduced prevalence of POI in the treated group, FSH concentrations were lower than in the control group at both 12 and 24 months ($P = 0.027$, $P = 0.001$, respectively).

There was a marked fall in AMH in both groups during treatment to median values of ∼5% of pretreatment levels in the

Table 2. Primary outcome analysis, presented both as amenorrhoea only, and POI (amenorrhoea with elevated FSH)

Age group	Outcome	Chemotherapy alone	Chemotherapy plus goserelin	Total	*P*	Worst case imputation	Best case imputation
Outcome: amenorrhoea between 12 and 24 months							
All	No amenorrhoea	66	74	140			
		61.7%	77.9%	69%			
	Amenorrhoea	41	21	62			
		38.3%	22.1%	31%			
	Total	107	95	202	0.015	0.017	0.024
≤40	No amenorrhoea	44	54	98			
		74.6%	90.0%	82%			
	Amenorrhoea	15	6	21			
		25.4%	10.0%	18%			
	Total	59	60	119	0.032		
>40	No amenorrhoea	22	20	42			
		45.8%	57.1%	51%			
	Amenorrhoea	26	15	41			
		54.2%	42.9%	49%			
	Total	48	35	83	0.376		
Outcome: POI							
All	No POI	43	53	96			
		65.2%	81.5%	73.3%			
	POI	23	12	35			
		34.8%	18.5%	26.7%			
	Total	66	65	131	0.048		
≤40	No POI	24	38	62			
		80.0%	97.4%	89.9%			
	POI	6	1	7			
		20.0%	2.6%	10%			
	Total	30	39	69	0.038		
>40	No POI	19	15	34			
		52.8%	57.7%	54.8%			
	POI	17	11	28			
		47.2%	42.3%	45.2%			
	Total	36	26	62	0.798		

control group and to 7% in the goserelin group (Figure 2), changes that were not significantly different between groups.

Logistic regression analysis was performed to assess the predictive value of factors associated with amenorrhoea (supplementary Table S1, available at *Annals of Oncology* online). Pretreatment AMH was shown to be a predictor of post-treatment amenorrhoea (odds ratio 0.43, 95% confidence interval [CI] 0.23–0.80, $P = 0.01$), as was age (OR 1.28, CI 1.18–1.39, $P < 0.001$), although after adjustment for age, the effect of pretreatment AMH was no longer significant. Total cyclophosphamide dose was not predictive (OR 1.15, CI 0.99–1.34, $P = 0.07$).

Discussion

Our results demonstrate that the use of the GnRH analogue goserelin provides some protection of ovarian function during chemotherapy for early breast cancer. The effect appears age-dependent, being less clear for women who are older than 40 years. It may be that the relative sample sizes in the two age cohorts accounts for some of this difference, accentuated by the slight randomization imbalance in the older age group. Results of AMH analysis, albeit only in a subgroup, demonstrated a very marked fall in this marker of the ovarian reserve in all women, and thus any protection of ovarian reserve is likely to be small.

There remains uncertainty concerning the efficacy or otherwise of trying to protect ovarian function from chemotherapy with GnRH-agonist mediated gonadotrophin suppression [17]. The present data are comparable with the results of some but not all RCTs of GnRH analogue treatment for the prevention of ovarian toxicity from chemotherapy. Two recent meta-analyses came to different conclusions: one, of 12 RCTs including 1231 breast cancer patients indicated that GnRH analogue treatment reduced the risk of POI (OR 0.36, 95% CI 0.23–0.57) although significant heterogeneity between study results was identified [10]. The second, of 10 trials including 907 women, concluded that GnRH analogues did not increase the proportion of women with ovarian function after chemotherapy with a risk ratio of 1.12, 95% CI 0.99–1.27 [9]. Additionally, GnRH analogue use in women receiving chemotherapy for lymphoma show inconsistent results [11, 12]. The use of GnRH analogues to protect ovarian function has however been endorsed by the 2015 St Gallen International

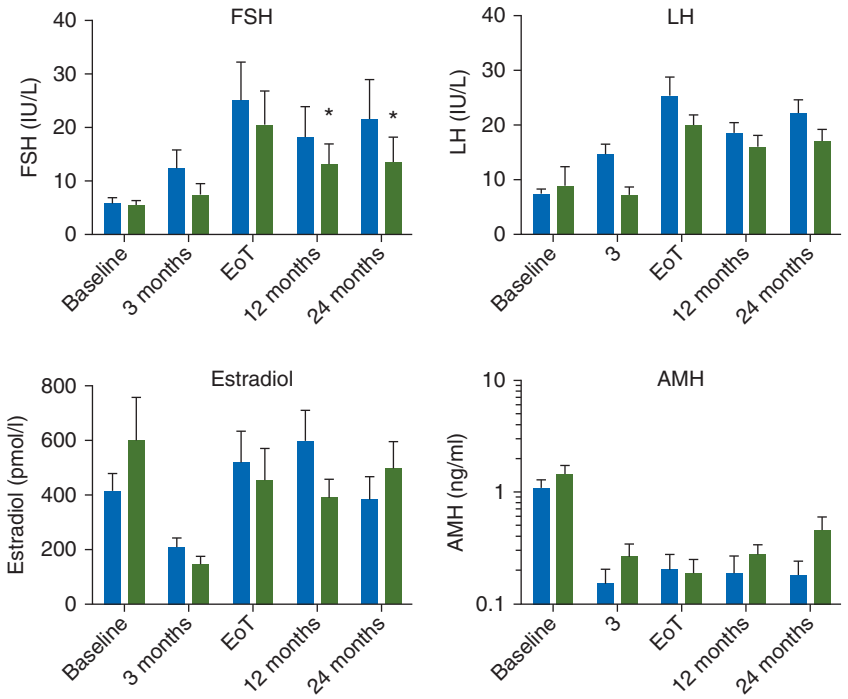

Figure 2. Hormonal evaluation. Blue, control group; green, goserelin group, data are shown as mean ± SEM. Note that AMH is shown on a log10 scale to allow the very low concentrations during and post-chemotherapy to be more clearly shown. EoT: end of chemotherapy treatment. *$P = 0.027$, $P = 0.001$ versus control group at 12 and 24 months, respectively. Sample size for control group 59–107 for FSH, LH, E2 and 37–56 for AMH; for Goserelin group, 63–96 and 36–53, respectively.

Consensus Panel [18] and for women with hormone receptor negative breast cancer in the guidelines of the National Comprehensive Cancer Network. This study provides substantial additional confidence in this effect, being the second largest trial reported, but suggests that any benefits are largely confined to women aged <40 years.

The mechanism whereby GnRH analogues might provide ovarian protection is unclear. Loss of growing follicles due to the effects of chemotherapy may additionally remove local inhibitory influences on the activation of growth of primordial follicles, thus accelerating depletion of the ovarian reserve [19]. There are also both mouse and non-human primate experimental data indicating a protective effect of GnRH analogues [20, 21].

In this and previous similar trials the primary outcome measure has been ovarian function as revealed by amenorrhoea or POI. These measures do not assess loss of the follicle pool within the ovary. AMH is a marker of the number of small growing follicles in the ovary, and indirectly reflects the number of primordial follicles (the 'ovarian reserve') [13]. In women with breast cancer, pretreatment AMH (with age) predicts remaining ovarian function after chemotherapy [15]. Post-treatment AMH indicates the degree of loss of ovarian reserve [14, 22] as women who retain ovarian function after chemotherapy are still likely to experience an early menopause [23]. Analysis of AMH post-chemotherapy may be of value in predicting remaining reproductive lifespan. The degree of fall in AMH shown here highlights the magnitude of the ovarian damage even in those without POI, with AMH at 2 years being reduced by 95% in the control group and by 93% in the goserelin group, although sample collection was incomplete. Thus the amount of 'saved' ovarian function is modest, but may be of clinical consequence particularly in younger women where it might allow an increased opportunity for fertility. Longer term benefits from any reduction in the consequences of estrogen deficiency have yet to be investigated.

Age and AMH were predictive of amenorrhea, the latter not being significant when adjusted for age. This is consistent with previous analyses of AMH as a predictor of post-chemotherapy ovarian function [15], and the importance of age in that context [24, 25]. This supports the concept that the size of an individual woman's ovarian reserve as well as her age determines her risk of POI following chemotherapy.

Additional data from a bone sub-study of this trial also suggested that goserelin provides some degree of ovarian protection from chemotherapy. Although the addition of goserelin to chemotherapy increased bone turnover during treatment, the return of bone biomarkers to the normal range after cessation of treatment was more frequent with goserelin and suggested that it may offer sufficient ovarian protection against chemotherapy-induced POI to negate the long-term altered bone turnover associated with POI [26].

Although the number of recurrences in our study are too few for meaningful comparison, the results of other trials that included mostly hormone-receptor positive breast cancer have been encouraging in respect of safety and efficacy [10], an important observation given the apparent survival benefit associated with chemotherapy-induced amenorrhoea in women with estrogen receptor positive breast cancer [27].

We conclude that the impact of using a GnRH analogue moderately reduces the risk of POI induced by standard adjuvant chemotherapy for early breast cancer in young women, but that this effect is uncertain for women over 40 years old.

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Disclosure

RL has undertaken consultancy work for Amgen, Pfizer, Novartis, Roche, Teva, Caris; GB has undertaken consultancy work for Eisai, Genomic Health, Pfizer, Novartis; JM has undertaken consultancy work for Puma biotechnology; AY has undertaken consultancy work for Kyowa Kirin, Emergent, Galderma, Immodulan, Ipsen, Leica, Pharmagenesis, ReNeuron, Shield, Tokai; RC received research funding from Bayer, Amgen to his institution; RAA has undertaken consultancy work for Roche Diagnostics. The other authors have no conflicts to disclose.

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