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

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1 **Article type: Original article**

2

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

5

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26

27

28

29 **Abstract**

30

31 **Background**

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

36

37 **Patients and Methods**

38 This was a prospective, randomized, parallel group study of the GnRH agonist goserelin  
39 administered before and during chemotherapy for breast cancer with stage I-III B disease. The  
40 primary outcome was amenorrhoea between 12 and 24 months after randomization, supported  
41 by elevated follicle stimulating hormone (FSH) concentrations to give an additional analysis as  
42 rate of POI.

43

44 **Results**

45 A total of 227 patients were randomized and the primary analysis was conducted on 202  
46 patients. Goserelin reduced the prevalence of amenorrhoea between 12 and 24 months to  
47 22% vs 38% in the control group ( $P=0.015$ ) and the prevalence of POI to 18.5% vs 34.8% in  
48 the control group ( $P=0.048$ ). FSH concentrations were also lower in all women treated with  
49 goserelin at both 12 and 24 months ( $P = 0.027$ ,  $P = 0.001$  respectively). The effect of goserelin  
50 was not statistically significant in women  $>40$  years. Assessment of the ovarian reserve using  
51 anti-Müllerian hormone (AMH) showed a marked fall in both groups during treatment to median  
52 values of 5% of pretreatment levels in the control group and 7% in the goserelin group, which  
53 were not significantly different between groups.

54

55 **Conclusion**

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

60

61 **Trial registration:** EudraCT 2004-000133-11

62

63 **Key message**

64 This RCT of GnRH agonist administration during chemotherapy for early breast cancer for  
65 ovarian protection showed a benefit in women aged under 40 years, but with no detected  
66 benefit in older women. The use of a biomarker of the ovarian reserve indicated that the  
67 amount of ovarian function preserved by this approach may be small.

68

69 **Introduction**

70

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

77 A number of observational studies have suggested a benefit from GnRH agonist suppression  
78 of ovarian function, but the data from randomized controlled trials (RCTs) remain mixed [3-7].  
79 The most recent substantial RCT in women with breast cancer [8] found evidence of reduced  
80 risk of ovarian failure with goserelin treatment during chemotherapy, and meta-analyses also  
81 report varying results [9, 10]. Trials in women with Hodgkin lymphoma also report varying results  
82 [11, 12].

83

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

91 Anti-Müllerian hormone (AMH) is also a valid and valuable marker of ovarian follicle reserve  
92 [13]. Pre-treatment AMH has been suggested to predict long term ovarian function following  
93 chemotherapy for early breast cancer, and post-treatment concentrations are an indicator of  
94 the remaining ovarian reserve in women who maintain menstrual function, thus providing a  
95 quantitative estimate of the degree of ovarian protection [14, 15].

96

97 **Patients and Methods**

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

115  
116 Randomization was centrally performed by telephone to the trial center, eligibility was  
117 confirmed verbally, and treatment was allocated by computer-generated lists. Pre-treatment  
118 evaluation included history and physical examination, haematology and biochemistry profiles,  
119 chest x-ray, electrocardiograph, and measurements of estradiol, FSH, and luteinizing hormone  
120 (LH) which were performed locally; serum was also stored for later measurement of AMH which  
121 was performed centrally using the Roche Elecsys automated assay.

122

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

126

## 127 **Statistical analysis**

128 The primary outcome was the rate of amenorrhea ie no menses between 12 and 24 months  
129 after randomization, also combined with elevated FSH concentrations to give rate of POI. For  
130 the sample size calculation, it was assumed that the rate of amenorrhea would be 40% in the  
131 40 years and under age-group and 80% in the over 40 age-group. At the time of conception of  
132 the trial, two uncontrolled studies had suggested that goserelin might reduce the rate of  
133 premature menopause to 20%. A one-sided test with 5% false-positive rate was used to  
134 calculate the sample size to give an 80% chance of detecting an absolute reduction from 40%  
135 to 20% in the 40 years and under group and from 80% to 55% in the older age group. It was  
136 intended to recruit a total of 250 patients and allowing for a 15% loss to follow-up.  
137 Randomization was stratified by age (aged 40 years or younger and those over 40 years) and  
138 by center.

139

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

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

150

151 **Results**

152

153 227 patients were randomized between 26 August 2004 and the end of December 2009. Of  
154 these, 3 in each arm were omitted from this analysis because they had died within 24 months  
155 of randomization and had therefore unknown menstrual status at 24 months. The age  
156 distribution, chemotherapy regimens and ER status for these 221 patients are described in  
157 Table 1, and did not differ between the 2 groups. For a further 19 patients (11 in the control  
158 arm and 8 in the intervention arm), menstrual status during the interval between the 12 month  
159 follow up visit and the 24 month follow up visit could not be determined from the data available.  
160 The primary analysis was therefore conducted on 202 patients (figure 1).

161

162 **Primary outcome**

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

166

167 The main outcome of this trial showed a difference in the prevalence of amenorrhoea between  
168 12 and 24 months, being 22% in the goserelin group vs 38% in the control group ( $P = 0.015$ ,  
169 table 2). After imputing missing data both as worst case (all with amenorrhoea) or best case  
170 (none with amenorrhoea) scenarios, there remained significant differences between groups,  
171 with reduced prevalence of amenorrhoea in the goserelin group (table 2). This apparent  
172 protective effect of goserelin was further assessed using the definition of POI ie amenorrhoea  
173 with elevated FSH concentrations using a FSH cutoff of 25IU/L [16]. The prevalence of POI in  
174 the goserelin group was 18.5% vs 34.8% in the control group ( $P = 0.048$ ), thus closely mirroring  
175 the amenorrhoea results.

176

177 Given the likely importance of age in determining risk of chemotherapy-related amenorrhoea,  
178 groups were stratified by age, using a cutoff of 40 years. This analysis showed a protective



179 effect of goserelin on both the prevalence of amenorrhoea alone and on POI (amenorrhoea  
180 plus high FSH) in women aged  $\leq 40$  (amenorrhoea: 10.0% vs 25.4%,  $P = 0.032$ ; POI: 2.6% vs  
181 20.0%,  $P=0.038$ ). The effect was less clear and not statistically significant in women  $>40$  years  
182 (amenorrhoea: 42.9% vs 54.2%,  $P = 0.376$ ; POI: 42.3% vs 47.2%,  $p=0.798$ ).

183

184 Nine pregnancies occurred in women in the goserelin group (including 2 pregnancies each for  
185 2 women) and 6 in the control group (including 2 pregnancies in one woman). A total of 24  
186 deaths occurred, 9 in the goserelin group and 15 in the control group.

187

### 188 **Hormonal evaluations**

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

195 There was a marked fall in AMH in both groups during treatment to median values of  
196 approximately 5% of pretreatment levels in the control group and to 7% in the goserelin group  
197 (figure 2), changes that were not significantly different between groups.

198

199 Logistic regression analysis was performed to assess the predictive value of factors associated  
200 with amenorrhoea (supplementary table 1). Pretreatment AMH was shown to be a predictor  
201 of post-treatment amenorrhoea (odds ratio 0.43, 95% confidence interval [CI] 0.23-0.80,  
202  $P=0.01$ ), as was age (OR 1.28, CI 1.18-1.39,  $P<0.001$ ), although after adjustment for age, the  
203 effect of pretreatment AMH was no longer significant. Total cyclophosphamide dose was not  
204 predictive (OR 1.15, CI 0.99-1.34,  $P = 0.07$ ).

205

### 206 **Discussion**

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

214

215 There remains uncertainty concerning the efficacy or otherwise of trying to protect ovarian  
216 function from chemotherapy with GnRH-agonist mediated gonadotrophin suppression [17].  
217 The present data are comparable with the results of some but not all RCTs of GnRH analogue  
218 treatment for the prevention of ovarian toxicity from chemotherapy. Two recent meta-analyses  
219 came to different conclusions: one, of 12 RCTs including 1231 breast cancer patients indicated  
220 that GnRH analogue treatment reduced the risk of POI (OR 0.36, 95% CI 0.23-0.57) although  
221 significant heterogeneity between study results was identified [10]. The second, of 10 trials  
222 including 907 women, concluded that GnRH analogues did not increase the proportion of  
223 women with ovarian function after chemotherapy with a risk ratio of 1.12, 95% CI 0.99-1.27 [9].  
224 Additionally, GnRH analogue use in women receiving chemotherapy for lymphoma show  
225 inconsistent results [11, 12]. The use of GnRH analogues to protect ovarian function has  
226 however been endorsed by the 2015 St Gallen International Consensus Panel [18] and for  
227 women with hormone receptor negative breast cancer in the guidelines of the National  
228 Comprehensive Cancer Network. This study provides substantial additional confidence in this  
229 effect, being the second largest trial reported, but suggests that any benefits are largely  
230 confined to women aged <40 years.

231

232 The mechanism whereby GnRH analogues might provide ovarian protection is unclear.. Loss  
233 of growing follicles due to the effects of chemotherapy may additionally remove local inhibitory  
234 influences on the activation of growth of primordial follicles, thus accelerating depletion of the

235 ovarian reserve [19]. There are also both mouse and non-human primate experimental data  
236 indicating a protective effect of GnRH analogues [20, 21] .

237

238 In this and previous similar trials the primary outcome measure has been ovarian function as  
239 revealed by amenorrhoea or POI. These measures do not assess loss of the follicle pool within  
240 the ovary. AMH is a marker of the number of small growing follicles in the ovary, and indirectly  
241 reflects the number of primordial follicles (the 'ovarian reserve') [13]. In women with breast  
242 cancer, pretreatment AMH (with age) predicts remaining ovarian function after chemotherapy  
243 [15]. Post-treatment AMH indicates the degree of loss of ovarian reserve [14, 22] as women  
244 who retain ovarian function after chemotherapy are still likely to experience an early  
245 menopause [23]. Analysis of AMH post chemotherapy may be of value in predicting remaining  
246 reproductive lifespan. The degree of fall in AMH shown here highlights the magnitude of the  
247 ovarian damage even in those without POI, with AMH at 2 years being reduced by 95% in the  
248 control group and by 97% in the goserelin group, although sample collection was incomplete.  
249 Thus the amount of 'saved' ovarian function is modest, but may be of clinical consequence  
250 particularly in younger women where it might allow an increased opportunity for fertility. Longer-  
251 term benefits from any reduction in the consequences of estrogen deficiency have yet to be  
252 investigated.

253

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

259

260 Additional data from a bone sub-study of this trial also suggested that goserelin provides some  
261 degree of ovarian protection from chemotherapy. Although the addition of goserelin to  
262 chemotherapy increased bone turnover during treatment, the return of bone biomarkers to the

263 normal range after cessation of treatment was more frequent with goserelin and suggested  
264 that it may offer sufficient ovarian protection against chemotherapy-induced POI to negate the  
265 long term altered bone turnover associated with POI [26].

266

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

272

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

276

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280 decision to publish the results. We are grateful for the support of colleagues in the Anglo Celtic  
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282

### 283 **Disclosures**

284 RL has undertaken consultancy work for Amgen, Pfizer, Novartis, Roche, Teva, Caris; GB has  
285 undertaken consultancy work for Eisai, Genomic Health, Pfizer, Novartis; JM has undertaken  
286 consultancy work for Puma biotechnology; AY has undertaken consultancy work for Kyowa  
287 Kirin, Emergent, Galderma, Immodulan, Ipsen, Leica, Pharmagenesis, ReNeuron, Shield,  
288 Tokai; REC has undertaken consultancy work for Bayer, Amgen; RAA has undertaken  
289 consultancy work for Roche Diagnostics. The other authors have no conflicts to disclose.

290

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372  
  
373  
  
374

375 **Figures legends**

376

377 Figure 1. Consort diagram showing disposition of patients recruited.

378

379 Figure 2. Hormonal evaluation. Blue, Control group; red, Goserelin group, data are shown as  
380 mean± sem. Note that AMH is shown on a log<sub>10</sub> scale to allow the very low concentrations  
381 during and post chemotherapy to be more clearly shown. EoT: end of chemotherapy treatment.

382 \*  $P = 0.027$ ,  $P = 0.001$  vs control group at 12 and 24 months respectively. Sample size for  
383 Control group 59-107 for FSH, LH, E2 and 37-56 for AMH; for Goserelin group, 63-96 and 36-  
384 53 respectively.