Goserelin with chemotherapy to preserve ovarian function in pre-menopausal women with early breast cancer: menstruation and pregnancy outcomes

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Background: Premature ovarian failure and infertility following chemotherapy in early breast cancer (EBC) are major concerns for young women. The role of gonadotrophin-releasing hormone (GnRH) agonists with chemotherapy in EBC in reducing the incidence of chemotherapy-induced early menopause remains uncertain, and long-term data on the recovery of fertility are sparse. We report an audit of our experience with the GnRH agonist, goserelin (Zoladex®), used with chemotherapy to preserve ovarian function and maintain fertility.

Patients and methods: Pre-menopausal women were given goserelin subcutaneously every 28 days during chemotherapy, starting 0–14 days before treatment. The main clinical end point was recovery of menstruation after chemotherapy. The other end points were rate of successful conception and median time to recovery of menses.

Results: About 84% of 125 women recovering menstruation with the median time to recovery of 6 months (1–43 months), including 76% of 71 patients aged over 35. Of the 42 patients who attempted pregnancy, 71% (n = 30) managed to achieve pregnancies. At the time of analysis, there were 42 pregnancies and 30 healthy deliveries.

Conclusions: The GnRH agonist, goserelin, given with chemotherapy for EBC is associated with a low risk of long-term chemotherapy-induced amenorrhoea and a high chance of pregnancy. Further randomised trials are needed.

Key words: early breast cancer, goserelin, ovarian protection
**Introduction**

The use of adjuvant chemotherapy in younger women with early breast cancer (EBC) has substantially improved the long-term outcome [1]. However, this benefit is associated with long-term toxic effects which are becoming more important as prognosis improves. These include premature menopause and infertility in young pre-menopausal women.

The incidence of premature menopause depends on the type and intensity of chemotherapy and the patient’s age. In women <35 years old, the long-term (3 years after diagnosis) incidence of amenorrhea is similar to women who have not received chemotherapy, at ~10%, but this increases to 50% in women between 35 and 40 years old, and can be up to 85% in women >40 years [2]. Premature ovarian failure has major consequences including sexual dysfunction and infertility, and the latter may be of great concern to younger patients with breast cancer and has a bearing in influencing treatment decisions in almost 30% of cases [3].

Currently, there is no standard treatment for preventing chemotherapy-induced ovarian failure. Previous studies have suggested that temporary ovarian suppression with a gonadotrophin-releasing hormone (GnRH) analogue may preserve ovarian function both in humans and animal models [4–9]. Clinical data are conflicting. For example, a recent Italian multi-centre phase III study Prevention of Menopause-Induced by Chemotherapy: A Study in Early Breast Cancer Patients—Gruppo Italiano Mamella 6 (PROMISE-GIM6) reported that the use of GnRH analogue, triptorelin during chemotherapy in pre-menopausal patients with EBC, reduced the occurrence of chemotherapy-induced early menopause with four pregnancies after a 26-month follow-up [one in the chemotherapy alone arm and three in the triptorelin with chemotherapy arm] [10]. In contrast, another trial suggested that the use of goserelin concurrently with neoadjuvant chemotherapy did not significantly reduce incidence of amenorrhea 6 months after the end of chemotherapy compared with those receiving chemotherapy alone and only two pregnancies were recorded [one in each arm] with a follow-up of 2 years [11]. Our institution has also previously published a series of 51 patients showing that the use of goserelin together with chemotherapy is associated with high rates of ovarian preservation and with eight pregnancies recorded in 10 women [12]. We have now updated this to 132 patients, with longer follow-up. To our knowledge, this is the largest series with long-term follow-up looking at the use of GnRH analogue, goserelin, with chemotherapy in the preservation of ovarian function and in pregnancy outcomes.

**Patients and Methods**

Eligible patients were pre-menopausal women up to the age of 45 years old treated at the Royal Marsden Hospital Breast Unit, London, with adjuvant or neoadjuvant chemotherapy for EBC with at least a 4-month follow-up from the completion of chemotherapy treatment or until death of patient. Consecutive patients were identified from a prospective database and, among them, all the patients who were anxious about preserving fertility were offered goserelin, excluding those who received any chemotherapy before goserelin, and those with a diagnosis of infertility before chemotherapy. No other hormonal treatments were allowed while receiving chemotherapy.

Between June 2001 and March 2009, patients identified were cross-referenced with the pharmacy database of patients receiving goserelin. Goserelin (Zoladex*, AstraZeneca, United Kingdom) 3.6 mg was given by subcutaneous injection every 28 days starting between 0 and 14 days before the first chemotherapy cycle, and the last injection was administered between 7 days before and up to 21 days after the last cycle of chemotherapy. All the patients who were oestrogen receptor (ER) positive were commenced on tamoxifen as adjuvant therapy for a planned duration of 5 years upon the completion of chemotherapy. For patients who intended to attempt pregnancy, our advice is to stop adjuvant tamoxifen for at least 2 months before attempting and to resume tamoxifen after pregnancy (and lactation) is completed, with the planned duration of 5 years of treatment in total. Pre-menopausal women, particularly when the tumour is ER positive, in which amenorrhea developed as a result of chemotherapy have better overall survival and disease-free survival [13, 14]. Thus, the patients who had shown recovery of menstruation were also given the option of restarting goserelin for a further 2 years or until they wish to attempt pregnancy.

Resumption of menstruation is defined as the first month of resumed menses in those patients who went on to have two or more consecutive spontaneous menstrual cycles. Data on menstruation were recorded 3-weekly during chemotherapy and 6-monthly afterward. Patients were also instructed to contact the Unit if menses restarted in the interim. To allow for collection of incomplete data, a minority of patients were sent a letter requesting permission to contact them to enquire about their menstrual function and fertility.

The main clinical end point was recovery of menstruation after chemotherapy and the other end points were rate of successful conception (number of patients achieving pregnancy divided by the total number of women actively attempting pregnancy) and median time to recovery of menses from the final dose of goserelin.

This study was conducted with local ethical committee approval to contact patients about return of menses and pregnancy attempts and outcomes.

**Results**

Between June 2001 and March 2009, 132 patients were recruited for this audit. The median age was 35 years with a range of 20–45 years (Table 1). About 71 of the 132 patients (54%) were ≥35 years. All the patients presented with primary invasive breast cancer and were eligible for surgical resection. About 69% (n = 91) of the patients had ER-positive tumours and 31% (n = 41) ER-negative disease. Nearly 67% (n = 88) of the patients received adjuvant chemotherapy following surgery and 33% (n = 44) neoadjuvant chemotherapy before surgery. At the time of this analysis, 70% of the patients (n = 93) were recurrence-free; of those patients, 68% (n = 63) had ER-positive disease and 32% (n = 30) had ER-negative disease. About 15% of the patients (n = 20) had died at the time of analysis.

Seven patients (5%) were considered non-assessable as they elected to continue goserelin without a break after the end of their chemotherapy.

Of the remaining 125 patients, the median follow-up after the last injection of goserelin was 58 months (range 4–119 months). The most commonly used schedule, given to 61 of...
125 (49%) of the patients, was the combination chemotherapy with 5-fluorouracil 600 mg/m², epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² [FEC] for six cycles at 3-weekly intervals. Table 2 shows the distribution of the types of chemotherapy regimens the patients received and Table 3 shows the cumulative doses of the administered cytotoxic agents. We have also looked the cumulative dose of cyclophosphamide in particular, as alkylating agents appear to carry the highest risk of ovarian failure [15], and found that there was no difference in the median cumulative dose of cyclophosphamide between those patients who remained amenorrhoeic and those whose menstruation resumed.

Of the 125 patients, 104 (84%) recovered menstruation with the median time to recovery of menses after the last goserelin injection at 6 months (1–43 months). The cumulative percentage of patients who resumed menstrual activity at 3 months was 21%, at 6 months was 54%, at 12 months was 82%, at 18 months was 94%, at 24 months was 95% and at 36 months was 99%. The median age of patients whose menstruation returned was 35 years (range 20–45 years) compared with 38 years (26–44 years) for those whose menstruation never returned (n = 20). The recovery rate of menses in patients under 35 years of age was 91% (51 of 56 patients), for ages 35–39 was 86% (44 of 51 patients) and for ≥40 years old was 56% (10 of 18 patients). Of the 71 patients who were ≥35 years, 54 patients (76%) had returned of menstruation. Twenty (16%) patients had goserelin restarted on return of menstruation; five patients underwent prophylactic oophorectomy including four patients because of BRCA mutation and one because of familial risk. Of the five patients who had undergone oophorectomy, four patients had resumed regular menstrual activity before deciding to go for prophylactic bilateral oophorectomy with only patient with a BRCA1 mutation who opted for oophorectomy before menstrual activity resumed. Of the patients with ER-positive disease (n = 91), all of them received adjuvant tamoxifen except for four patients (0.04%) who refused adjuvant tamoxifen at the outset. At the time of analysis, 27 patients were still on adjuvant endocrine therapy.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>132</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>35 (20–45)</td>
</tr>
<tr>
<td>Age distribution (years)</td>
<td></td>
</tr>
<tr>
<td>20–24</td>
<td>1</td>
</tr>
<tr>
<td>25–29</td>
<td>24</td>
</tr>
<tr>
<td>30–34</td>
<td>36</td>
</tr>
<tr>
<td>35–39</td>
<td>53</td>
</tr>
<tr>
<td>40–45</td>
<td>18</td>
</tr>
<tr>
<td>Receptor status</td>
<td></td>
</tr>
<tr>
<td>ER positive</td>
<td>91 (69)</td>
</tr>
<tr>
<td>ER negative</td>
<td>41 (31)</td>
</tr>
<tr>
<td>Treatment type</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>88 (67)</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>44 (33)</td>
</tr>
</tbody>
</table>

ER, oestrogen receptor.

Table 2. Chemotherapy regimens

<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anthracycline and cyclophosphamide</td>
<td>75</td>
</tr>
<tr>
<td>Fluorouracil, epirubicin and cyclophosphamide</td>
<td>61</td>
</tr>
<tr>
<td>Doxorubicin/epirubicin and cyclophosphamide</td>
<td>14</td>
</tr>
<tr>
<td>2. Anthracycline and cyclophosphamide followed by taxanes</td>
<td>46</td>
</tr>
<tr>
<td>Anthracycline cyclophosphamide–paclitaxel</td>
<td>23</td>
</tr>
<tr>
<td>Anthracycline cyclophosphamide–docetaxel</td>
<td>23</td>
</tr>
<tr>
<td>3. Others</td>
<td>4</td>
</tr>
<tr>
<td>Docetaxel and cyclophosphamide</td>
<td>1</td>
</tr>
<tr>
<td>Capecitabine and epirubicin</td>
<td>1</td>
</tr>
<tr>
<td>Epirubicin and cyclophosphamide–paclitaxel and gemcitabine</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3. Cumulative dose of administered cytotoxic agents

<table>
<thead>
<tr>
<th>Cytotoxic agent</th>
<th>Number of patients</th>
<th>Median in mg/m² (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil</td>
<td>75</td>
<td>3600 (1020–3600)</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>81</td>
<td>360 (128–470)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>124</td>
<td>3215 (1036–3600)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>43</td>
<td>240 (120–360)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>25</td>
<td>300 (200–600)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>25</td>
<td>700 (350–700)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>2</td>
<td>1000 (1000–1000)</td>
</tr>
</tbody>
</table>

A Mann–Whitney non-parametric test shows no significant difference (P = 0.503) in the dose level of cyclophosphamide between patients whose menstruation returned and those whose menstruation did not return.

pregnancy

Nearly 57 patients (46% of the 125 assessable patients) were interested in getting pregnant. About 42 patients (74% of the patients who were interested in getting pregnant) have so far attempted pregnancy and 30 of these (71% of the patients who attempted pregnancy) have managed to achieve pregnancies, 2 of whom through assisted fertility with donor eggs. There were 42 pregnancies among 30 patients of which 30 were healthy deliveries at the time of analysis with three pending deliveries. The median time to achieving pregnancy from the onset of diagnosis of breast cancer was 40 months (range 12–93 months). Eight women aged ≥35 years managed to achieve pregnancies. There were five spontaneous miscarriages, three voluntary terminations for social reasons and one patient had an ectopic pregnancy. Only one patient of the 30 women who achieved pregnancies (0.03%) had a relapse of breast cancer after pregnancy.

No toxicity over that usually associated with chemotherapy was observed during the goserelin administration.

discussion

Fertility preservation is very important to many patients diagnosed with cancer. Chemotherapy is well established for increasing the risk of premature menopause. The risk depends
on the type and intensity of chemotherapy and the patient's age, with a risk of around 50% in women between 35 and 40 years old and up to 85% in women >40 years [2]. It has been postulated that GnRH analogues preserve ovarian function possibly by interruption of follicle-stimulating hormone secretion, decreasing in utero-ovarian perfusion or the protection of undifferentiated germ-line stem cells [16]. Data from animal models suggest that the use of GnRH agonists can decrease gonadal toxicity on testes and ovaries of mice and monkeys exposed to cyclophosphamide [4, 17].

A 94% rate of ovarian function preservation with this approach has been reported in women undergoing chemotherapy for lymphoma compared with 39% in the control group [5]. Likewise, the PROMISE-GIM6 randomised trial showed a 17% absolute reduction in the occurrence of early menopause in pre-menopausal women with breast cancer undergoing chemotherapy [10]. A smaller trial involving 78 patients aged 18–40 years with EBC randomised to receive chemotherapy alone or in combination with goserelin, found that the rate of premature ovarian failure in the two groups were 67% and 11%, respectively [18]. Another study (presented only in abstract), reported recovery of menstruation in 23 of 24 women after GnRH analogue therapy; their median age was 35 years (range 23–42 years) and they achieved recovery of menses a mean of 5.7 months after chemotherapy [7, 19]. A further study reported 64 patients with EBC with a median age of 42 years (range 27–50 years) receiving goserelin for 1 year with adjuvant treatment according to the patients' prognoses [20]. After a median follow-up of 55 months, 86% of the patients had resumed normal menses. In a subsequent update involving a total of 100 patients and a median follow-up of 75 months, only 67% of women recovered normal menses, and this included 100% of women under 40 and 56% of those over 40. In contrast, however, the ZORO (ZOladex Rescue of Ovarian function) study randomised 60 oestrogen-receptor-negative patients with breast cancer to anthracycline and taxane-containing chemotherapy alone or in combination with goserelin and found that there was no statistical difference in the outcome of resumption of ovarian function between the two groups [11]. The OPTION (Ovarian Protection Trial in Premenopausal Breast cancer patients) trial also found no difference in ovarian protection between patients randomised to chemotherapy alone or with goserelin, although the results are still preliminary [21]. Two other trials each involving 49 patients with breast cancer treated with or without goserelin during chemotherapy also found no statistical difference in the rates of amenorrhoea between the groups [22, 23]. A meta-analysis involving three other randomised and eight non-randomised prospective controlled studies, 10 of which involved patients with non-breast cancer diagnoses, showed that GnRH agonist during chemotherapy is associated with a greater likelihood of ovarian function preservation [odd ratio (OR) 10.57; 95% confidence interval (CI) 5.22–21.39]. However, when only the randomised studies were considered, there was no significant difference between those who received goserelin or not during chemotherapy [OR 5.76; 95% CI 0.47–71.03] [24].

Our analysis, involving the largest number of women with breast cancer so far, shows that the administration of the GnRH analogue, goserelin during chemotherapy is safe and is associated with a high rate of return of menstruation. Although our data are non-randomised, the incidence of recovery, and in particular in those over 35 (76% recovery of menses), is considerably higher than that reported in the literature [2].

The resumption of menstruation does not necessarily equate with fertility, but we have also shown in our series, with a long follow-up, that 71% of our patients who attempted pregnancies managed to achieve these with successful outcomes after the use of goserelin during chemotherapy. This is the largest series by far reporting specifically on pregnancies, with 42 pregnancies and 30 healthy deliveries, including eight women aged ≥35 years. It is worth noting that the majority of patients (54%) receiving goserelin to preserve fertility have not so far attempted pregnancy. This could be partly explained by the fact that the general advice of the treating physicians to patients is to delay pregnancy for at least the first 2–3 years as this is the time period when recurrence of breast cancer is the highest. Our results, however, make the point that what matters to most women is preserving the option for pregnancy rather than the pregnancy itself.

There is limited previous information on pregnancy outcomes after use of the GnRH agonists with chemotherapy. The PROMISE-GIM6 trial reported three pregnancies in the triptorelin with chemotherapy arm [10]. In the ZORO study, only two pregnancies were recorded [one in each arm] [11]. One study (presented only in abstract), reported five pregnancies in 6 of 24 patients after GnRH analogue therapy, with two live births, three miscarriages and one termination because of Down’s syndrome [7, 19]. In a larger study of 64 patients with EBC with a median age of 42 years (range 27–50 years) who received goserelin for 1 year with adjuvant chemotherapy, only one patient had a pregnancy which ended with a normal childbirth, within 5 years after treatment [20]. In a subsequent update involving a total of 100 patients and a median follow-up of 75 months, only three pregnancies were recorded [9].

Currently, the options for young women to avoid potential sterility following adjuvant or neoadjuvant chemotherapy include embryo cryopreservation and oocyte or ovarian cryopreservation. However, these procedures are costly, complex and have a significant failure rate [25, 26]. Both embryo and oocyte preservation techniques require ovarian stimulation before harvest with exposure to high oestrogen levels, a potential risk in patients with hormone-dependant tumours. In addition, these techniques involve the delay of 2–6 weeks in starting chemotherapy and require laparoscopy for general anaesthesia. Also the benefit in patients >40 years of age is uncertain [27]. Ovarian tissue cryopreservation and later transplantation also has a theoretical concern for potential reintroduction of cancer cells.

The use of GnRH analogues also has other advantages. A male partner is not required, the treatment is simple to administer at a fairly low cost and does not require delaying the start of chemotherapy. However, the use of GnRH analogues for ovarian suppression and cryopreservation are not mutually exclusive and can be used together to increase the chances of preserving fertility in young women who require...
chemotherapy [28], and this is one of the strategies currently offered in our institution.

The outcome benefit of ovarian suppression in addition to adjuvant chemotherapy is currently uncertain [13, 29–33]. We have therefore offered patients re-administration of goserelin at the time of ovarian function resumption for around 2 years or until the time at which pregnancy was to be attempted, to address this concern.

In conclusion, this is the largest series of premenopausal breast cancer patients treated with a GnRH agonist during chemotherapy in which the pregnancy rate and outcomes are reported. The high pregnancy rate (71% of the patients who attempted pregnancy achieved it) further supports the role of GnRH agonist in preserving ovarian function during chemotherapy for EBC patients. Larger randomised trials to address the issue further are warranted.

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disclosure

The authors have declared no conflicts of interest.

references

Conservative management of early-stage epithelial ovarian cancer: results of a large retrospective series

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Background: To assess the long-term oncological outcome and the fertility of young women with early-stage epithelial ovarian cancer (ES/EOC) treated with fertility-sparing surgery (FSS).

Patients and methods: All patients treated with FSS for ES/EOC in two Italian centers were considered for this analysis. Univariate and multivariate analyses were used to test demographic characteristics and clinical features for the association with overall survival (OS), recurrence-free survival (RFS) and fertility.

Results: From 1982 to 2010, 240 patients with malignant ES/EOC were treated with FSS in two tertiary centers in Italy. At a median follow-up of 9 years, 27 patients had relapsed (11%) and 11 (5%) had died of progressive disease. Multivariate analysis found only grade 3 negatively affected the prognosis of patients [hazard ratio (HR) for recurrence: 4.2, 95% confidence interval (CI): 1.5–11.7, P = 0.0067; HR for death: 7.6, 95% CI: 2.0–29.3, P = 0.0032]. Grade 3 was also significantly associated with extra-ovarian relapse (P = 0.006). Of the 105 patients (45%) who tried to become pregnant, 84 (80%) were successful.

Conclusions: Conservative treatment can be proposed to all young patients when tumor is limited to the ovaries, as ovarian recurrences can always be managed successfully. Patients with G3 tumors are more likely to have distant recurrences and should be closely monitored.

Key words: fertility-sparing surgery, obstetrical outcome, ovarian cancer, survival

Introduction

Epithelial ovarian cancer (EOC) is a postmenopausal disease, as it is more frequent in the fifth and sixth decades. Moreover, the majority of EOC patients are diagnosed when there is already abdominal spread of the disease. However, ~25% are limited to the ovaries at diagnosis, and 14% of invasive ovarian cancers are in women <40 years old [1].

Fertility-sparing surgery (FSS) for women of childbearing age with early-stage malignant epithelial ovarian cancer (ES/EOC) has been intensely debated in the last two decades. Preservation of the reproductive tract in young women who want children, especially if nulliparas, is a widely understood need, in light of the excellent prognosis of women with ES/EOC. Historically, hysterectomy and bilateral salpingo-oophorectomy have been considered part of the initial surgical approach to ovarian cancer, regardless of the stage of the disease. ESMO guidelines still recommend these procedures even for stage I to II ovarian cancer patients, though uterus preservation and unilateral salpingo-oophorectomy are admitted in selected cases. Preservation of the adnexa and uterus is currently recommended in patients with non-epithelial tumors and epithelial borderline ovarian cancer, but is still considered suboptimal for women with invasive EOC, and there is general concern about the greater risk of relapse for patients who preserve the uterus and ovaries [2, 3].

There are only a few published series about conservative management of ES/EOC [4–13], and none are conclusive, as no randomized clinical trial has yet been done and, for ethical and practical reasons, none is likely in the future. Therefore, it