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Suppression of ovarian function in combination with an aromatase inhibitor as treatment for advanced breast cancer in pre-menopausal women

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ABSTRACT

Trials have shown superiority of aromatase inhibitors (AIs) over tamoxifen for post-menopausal oestrogen receptor-positive advanced breast cancer (ER + ABC). We previously reported the use of goserelin plus anastrozole (G + A) as second-line endocrine therapy for pre-menopausal ER + ABC. We report clinical and endocrine data from G + A as first-line systemic therapy.

Thirty-six patients (median age = 44 years) with metastatic ($N = 28$) and locally advanced disease were administered G + A for $\geqslant 6$ months (unless progressed prior). Some ($N = 13$) received further therapy with goserelin plus another AI (steroidal), exemestane (G + E). Serial serum hormone assays (oestradiol, dehydroepiandrosterone sulphate, testosterone, follicle stimulating hormone and luteinising hormone) were performed.

Twenty-four patients (67%) derived clinical benefit (CB) (5% complete response, 31% partial response, 31% stable disease for $\geqslant 6$ months) with median time to progression and duration of CB of 12 (2–47) and 24 + (7–78+) months respectively. Ten patients were still receiving first-line G + A at analysis. Amongst 13 patients who went onto receive G + E, 38% achieved CB with a mean duration of 13+(7–32) months. Therapy was well tolerated with no withdrawals. The combination of G + A resulted in 98% reduction (from pre-treatment to 6-month) in median levels of oestradiol (from 574.5 pmol/L; inter-quartile range (IQR) = 209–1426; ($N = 6$) to 13.45 pmol/L; IOQ = 5.5–31.5 ($N = 4$) whilst the levels of other hormones had minimal fluctuations during therapy.

The combinations of ovarian function suppression (using G) and AIs produce sustained CB and minimal side effects in pre-menopausal ER + ABC with significant reduction in oestradiol levels. Within the limitations of being a non-randomised study, they should be considered in appropriate patients with hormone-sensitive ABC.

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1. Introduction

On 15th June 1895 George Beatson, a surgeon from Glasgow, performed bilateral salpingooophorectomy on a 33-year old woman with inoperable recurrent advanced breast cancer resulting in a complete response in 8 months.[1] Despite being a single case report, it illustrates and reminds us that endocrine therapy could work effectively in young pre-menopausal women with advanced breast cancer. Over the last century, the oestrogen receptor (ER) has since been discovered and tamoxifen has been used for more than three decades. Luteinising hormone releasing hormone (LHRH) agonists (e.g. goserelin) have been developed and shown to produce effective ovarian function suppression in the same way as surgical oophorectomy or ovarian irradiation.[2] Trials have confirmed the effectiveness of an LHRH agonist in combination with tamoxifen, in both advanced and adjuvant settings for pre-menopausal women with ER positive breast cancer.[3,4]

Phase II and III studies with the third generation aromatase inhibitors (AIs) (anastrozole, letrozole and exemestane) show comparable or superior clinical benefit (CB) and time to progression (TTP) compared with tamoxifen, when they were used to treat hormone receptor-positive advanced breast cancer in post-menopausal women.[5–8] Randomised trials have also confirmed their superiority over tamoxifen in terms of recurrence, disease-free survival, contralateral cancer, and in some situations overall survival, as an adjuvant endocrine therapy in early breast cancer[9] These AIs also show superior tolerability over tamoxifen in terms of thromboembolic and gynaecological events. In post-menopausal women, AIs have superseded tamoxifen as the treatment of choice for advanced breast cancer, and as an adjuvant systemic therapy for early disease in post-menopausal women with ER positive tumours.[9]

Oestradiol (E2) levels in pre-menopausal women are much higher than in post-menopausal women. The comparatively small effect of AIs interrupts the negative feedback control of follicle stimulating hormone (FSH) and LH and causes increased E2 secretion.[10] Increased E2 levels can cause tumour stimulation and follicular hyperplasia. Aromatase inhibitors alone are therefore not suitable for use in pre-menopausal women.

We have published the first report of using such a combination (goserelin plus anastrozole) as second-line endocrine therapy for ER positive pre-menopausal advanced breast cancer following disease progression on goserelin plus tamoxifen.[11] Twelve patients (75%) achieved objective response (OR) or durable stable disease (SD) at 6 months, with a median duration of remission of 17+ months (range 6–47 months). Introduction of goserelin and tamoxifen resulted in an 89% reduction in mean E2 levels (pre-treatment versus. 6 months = 224 vs. 24 pmol/L) ($p < 0.0001$). Substitution of tamoxifen by anastrozole on progression resulted in a further 76% fall (to 6 pmol/L at 3 months) ($p < 0.0001$).

Ovarian function suppression with goserelin could enable pre-menopausal women to be treated in the same way as post-menopausal women with respect to other endocrine therapies. The sequential use of different hormonal therapies in combination with goserelin may extend the opportunity for using well-tolerated endocrine treatments. This paper explores the subject further by reporting clinical and endocrine data when the combination of goserelin and anastrozole (a non-steroidal AI) is used as first-line systemic therapy for ER positive pre-menopausal advanced breast cancer. The continued use of goserelin to maintain ovarian function suppression in combination with a further AI (exemestane (a steroidal AI)) following prior treatment with anastrozole and/or tamoxifen will also be investigated.

The initial results of the study were first reported in abstract forms in 2005 and 2006.[12,13]

2. Patients and methods

2.1. Clinical study

All patients with advanced breast cancer (locally advanced primary or metastatic disease) were managed under a dedicated team of clinicians in a combined surgical/oncology facility. As per local treatment guidelines, the recommendation for endocrine therapy was made following multidisciplinary team discussion. Factors considered included ER positivity, disease-free interval, site of disease, symptoms, patient preference and response to previous endocrine therapy.[14]

2.1.1. Goserelin plus anastrozole as first-line systemic therapy

During the period of the study (2000–2007), goserelin (3.6 mg subcutaneously every 4 weeks) plus anastrozole (1 mg orally once daily) as a combination was the first-line endocrine therapy of choice in pre-menopausal women with ER positive advanced breast cancer. Patients who fulfilled the following criteria were included in this part of the study:

1. Pre-menopausal women at the time of diagnosis of advanced breast cancer (having normal menstrual periods or otherwise with ovarian function confirmed biochemically);
2. Biopsy proven ER positive (immunohistochemical (H) score of $\geqslant 50$) invasive breast carcinoma based on well established immunostaining index on a 0–300 scale;
3. Received goserelin plus anastrozole as first-line systemic therapy for advanced breast cancer;
4. Treatment lasted for $\geqslant 6$ months unless they progressed prior; and
5. Had disease assessable by UICC criteria.[15]

A total of 36 patients fulfilled these criteria and were included in this part of the study. Details of the sites of disease are summarised in Table 1. Endocrine therapy was considered treatment of choice for 34 patients. Two patients with liver metastases received endocrine therapy despite chemotherapy being treatment of choice – one patient refused chemotherapy, chemotherapy contraindicated in one patient due to pulmonary embolism. Results below are however presented based on all patients.

2.1.2. Continued goserelin plus another aromatase inhibitor

Some patients with advanced breast cancer in the same facility received further endocrine therapies, which contained a

Table 1 – Sites of disease for patients on goserelin plus an aromatase inhibitor for advanced breast cancer.

Site of disease	N (%) – first-line goserelin + anastrozole	N (%) – further lines goserelin + exemestane
Locally advanced primary	8 (22)	1 (8)
Metastatic	28 (78)	12 (92)
Bone	12 (34)	6 (46)
Lung/pleura	5 (14)	–
Bone + lung/pleura	3 (8)	4 (31)
Soft tissue	2 (5.5)	–
Liver ± bone/ lung/pleura	4 (11)	2 (15)
Others	2 (5.5)	–
Total	36 (100)	13 (100)

combination of goserelin (3.6 mg subcutaneously 4 weekly) and exemestane (25 mg orally once daily). They had to have fulfilled the same criteria as described above (except 3). In addition they should have received a combination of goserelin plus anastrozole prior. As such patients from the first part of this study who fulfilled these criteria were also included in this part.

A total of 13 patients fulfilled these criteria and were included in this part of the study. Details of the sites of disease are summarised in Table 1. They received goserelin plus exemestane as second ($N = 3$), third ($N = 6$) or fourth ($N = 4$) line endocrine therapy. As will be illustrated later, some of them received megestrol acetate (160 mg orally once daily) alone as endocrine therapy during the course of their treatment. Some also received goserelin plus tamoxifen at some point. None of them received intervening chemotherapy.

2.1.3. *Assessment of therapeutic responses*

For all patients, response status was defined as previously described for complete response (CR), partial response (PR), SD, progressive disease (PD), OR = CR + PR, and CB = CR + PR + SD for $\geqslant$6 months.[15,16] Duration of CB was calculated as the duration of the respective treatment in patients who achieved CB. Time to progression (TTP) was the time from commencing a treatment till PD; only patients who developed PD at the time of analysis were included in its calculation.

2.2. *Endocrine study*

Patients being treated in our facility were invited to donate blood samples for research purposes. Those who had consented and had sequential samples available during their endocrine therapy were included in this part of the study. They had to have included an AI given alongside goserelin at some stage of their treatment. The endocrine therapy agents used included goserelin plus tamoxifen, anastrozole, or exemestane, and megestrol acetate alone. Patients who received intervening chemotherapy were excluded. The blood samples were spun down with serum stored in 1 ml aliquots in the freezer (–20 °C). They were transported from Nottingham to London for hormone assays by a laboratory team who were blinded from the clinical information.

Serum E2 (up to 100 pmol/L), dehydroepiandrosterone sulphate (DHEAS) (0.8–7.0 μmol/L), testosterone (up to 2.8 nmol/L), FSH (23–132.9 U/L) and LH (15.9–72.6 U/L) levels were measured by standardised and sensitive (E2 only) hormone assays. The values in brackets represent normal cutoffs in post-menopausal (assuming similar effects with ovarian function suppression) women.

3. Results

3.1. *Clinical study*

3.1.1. *Goserelin plus anastrozole as first-line systemic therapy*

Out of 36 patients (median age = 44 (range 30–59) years), 24 patients (67%) achieved CB at 6 months (Table 2). The overall median duration of treatment was 18+ months (range 2–78 months) and the median TTP was 12 months (range 2–47 months). The median duration of CB was 24+ months (range 7–78+ months). Ten patients were still receiving therapy at the time of analysis. The treatment was well tolerated with no patients withdrawing due to adverse events.

3.1.2. *Continued goserelin plus another aromatase inhibitor*

Out of 13 patients (median age = 43 (range 33–54) years), five patients (38%) derived CB with a mean duration of CB of 13+ months (range 7–32 months). They had different combinations of endocrine agents prior to goserelin plus exemestane (Table 3). Overall, 12 of the 13 patients have now progressed with one patient still receiving treatment. Treatment was well tolerated and no patients discontinued due to adverse events.

Table 2 – Response status at 6 months on goserelin and anastrozole as first-line endocrine therapy for advanced breast cancer.

Response status at 6 months	Number (%)
CR	2 (5%)
PR	11 (31%)
SD	11 (31%)
CB (CR + PR + SD)	24 (67%)
PD	12 (33%)

CR, complete response; PR, partial response; SD, stable disease; CB, clinical benefit; PD, progressive disease.

Table 3 – Efficacy of goserelin plus exemestane as continued endocrine therapy.

Endocrine agents prior to G + E	Number	CB rate (%)	Mean duration of CB (months)
G + A	3	0	N/A
G + T → G + A	6	50	17
G + T → G + A → M	4	50	7

G, goserelin; A; anastrozole; E, exemestane; M, megestrol acetate; CB, clinical benefit; N/A, not applicable.

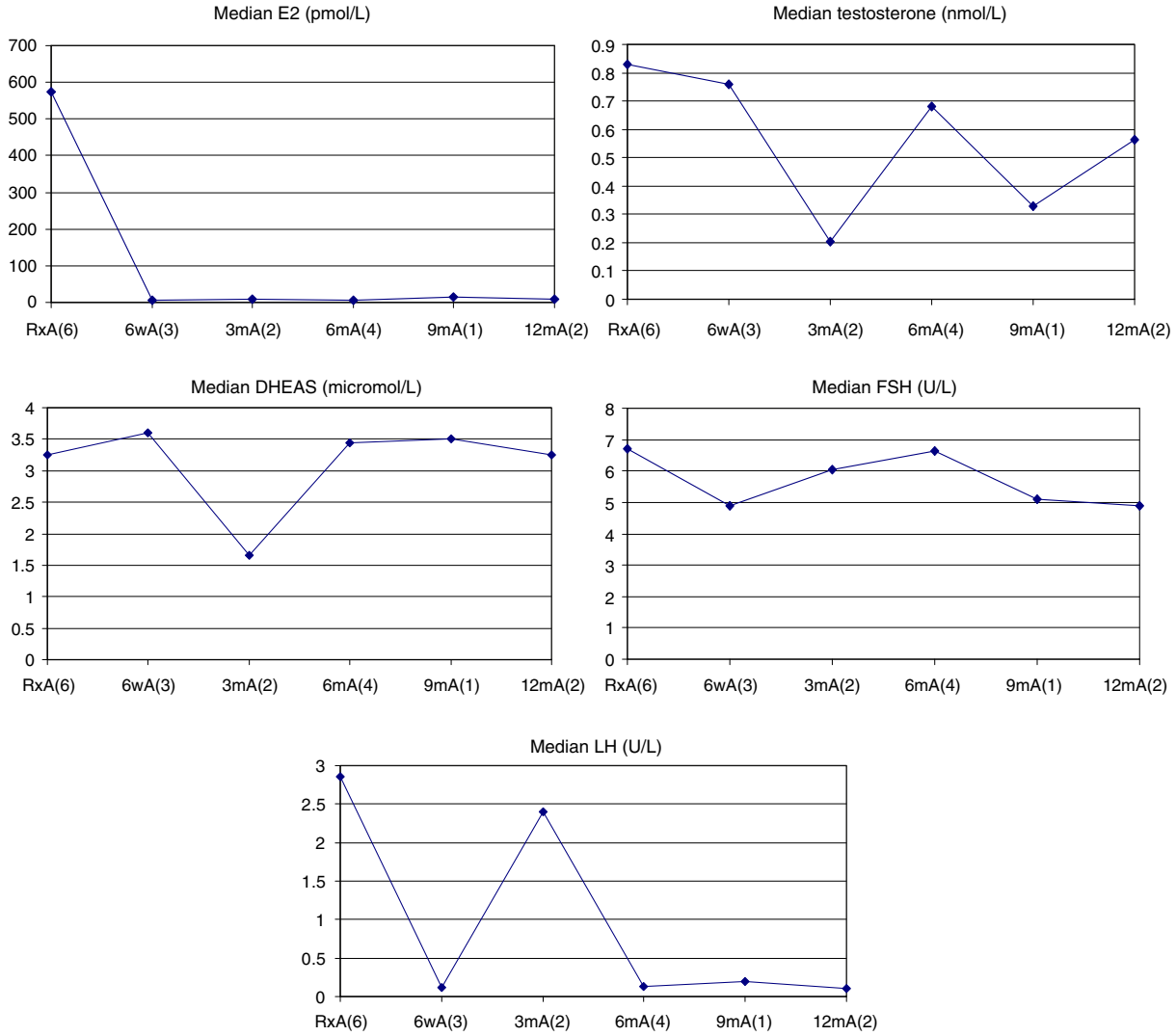

Fig. 1 – Changes of hormone levels with goserelin plus anastrozole as first-line endocrine therapy. Time points denoted on x-axis: Rx, pre-treatment; 6w, 6 weeks; 3m–6m–9m–12m, 3–6–9–12 months respectively; A, Goserelin + anastrozole; (), number of patient samples measured.

3.2. *Endocrine study*

A total of 93 serum samples from 22 patients were sent for hormone assays. The sequence of their treatments and the results of the hormone assays are summarised below.

3.2.1. *Goserelin plus anastrozole only*

The combination produced a drastic fall (98%) in median E2 level (pre-treatment to 6-month: from 574.5 pmol/L; interquartile range (IQR) = 209–1426; (*N* = 6) to 13.45 pmol/L; IOQ = 5.5–31.5 (*N* = 4) (Fig. 1). Some mild falls in other hormone levels were observed, though all of them (testosterone, DHEAS, LH and FSH) remained low.

3.2.2. *Goserelin plus anastrozole → goserelin plus exemestane*

3.2.2.1. *Goserelin plus anastrozole → goserelin plus tamoxifen.* Change of anastrozole at disease progression to exemestane whilst ovarian function suppression was maintained with goserelin did not result in any significant changes in the levels of all hormones measured (data not shown). Similarly no significant fluctuations were seen when anastrozole was changed to tamoxifen as second-line endocrine therapy (data not shown).

3.2.3. *Goserelin plus tamoxifen → goserelin plus anastrozole → goserelin plus exemestane*

The above sequence of treatment also did not lead to any significant fluctuation of the levels of all hormones measured, at the two time points when treatment was changed. All hormones concerned remained at low levels (data not shown).

3.2.4. *Goserelin plus tamoxifen → goserelin plus anastrozole → megestrol acetate only → goserelin plus exemestane*

Whilst the patients were receiving endocrine therapy in the above sequence, the levels of all hormone levels remained low. However, during the period when megestrol acetate

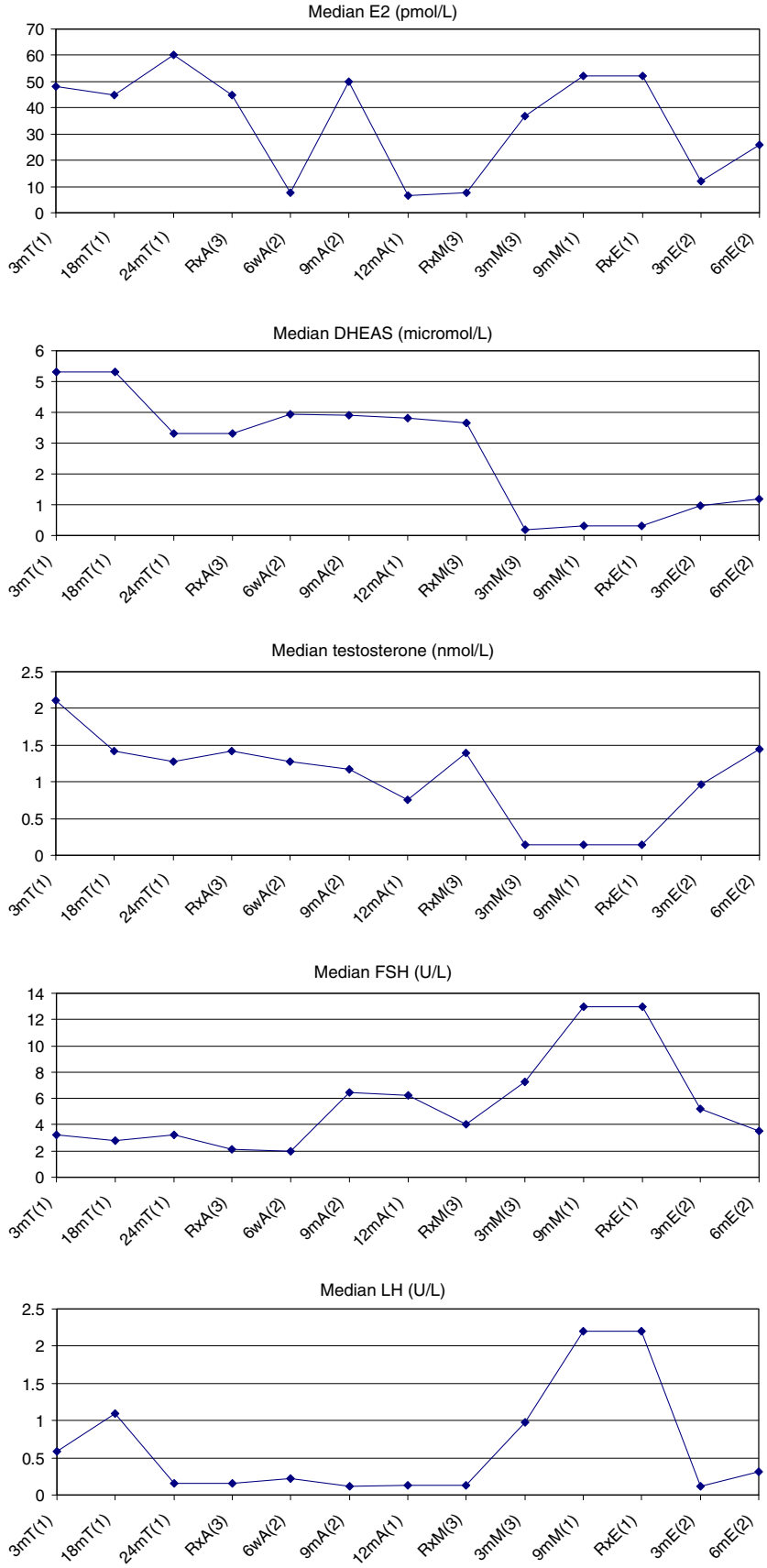

Fig. 2 – Changes of hormone levels with goserelin plus tamoxifen → goserelin plus anastrozole → megestrol acetate only → goserelin plus exemestane. Time points denoted on *x*-axis: Rx, pre-treatment; 6w, 6 weeks; 3m–6m–9m–12m–18m–24m, 3–6–9–12–18–24 months respectively; A, goserelin + anastrozole; T, goserelin + tamoxifen; A, goserelin + anastrozole; M, megestrol acetate only; E, goserelin + exemestane; (), number of patient samples measured.

was used on its own, there was a further reduction in testosterone and DHEAS levels and also a slight surge of FSH and LH levels (Fig. 2).

4. Discussion

Within the limitations of this study not being a randomised study and with small sample size, goserelin plus anastrozole appears to be an effective first- or second-line therapy for pre-menopausal women with ER positive advanced breast cancer. Subsequent treatment with goserelin plus exemestane also appears to be effective.

This is one of the three reports in the literature looking at the first-line use of goserelin plus anastrozole in pre-menopausal women with hormone receptor-positive advanced breast cancer. One of the other reports is from the United States involving 32 patients from two centres (Stanford University and MD Anderson Cancer Center).[17] It shows a 72% CB rate with a median TTP of 8 months. Another report is from a multi-centre study in France involving 33 patients showing a CB rate of 63.6% and TTP of 13 months.[18] The results are essentially similar though our report describes the same size of patients but from a single centre. Nonetheless there has not been any report on the continued use of goserelin to maintain ovarian function so that further use of another AI (e.g. a steroidal AI – exemestane as described in this study) is made possible. The present paper is the only report using such combination as the first systemic therapy for advanced breast cancer (no prior chemotherapy) with the longest follow-up (more than 6 years) from a single centre. Furthermore, whilst Carlson's study reported a similar drop in E2 level with treatment, our study has provided a full assessment of a number of hormones in this context. In addition, the extension of the concept with the further use of another AI was explored.

Goserelin plus anastrozole treatment was associated with a substantial reduction in oestradiol levels. Other hormones remained in low levels as long as ovarian function suppression was maintained using goserelin, when it was given alongside exemestane or tamoxifen as further endocrine therapy. Whilst the use of megestrol acetate in pre-menopausal women is not the subject of this paper, it was found to be associated with a different pattern of endocrine changes, when compared to the combined use of goserelin plus an AI.

No further significant drop in E2 level when tamoxifen was swapped to anastrozole was seen in this series as observed before.[11] This could be related to the small number of samples ($N = 2$) available for assays in this study.

In the advanced disease setting, there are no randomised data to show if goserelin plus an AI produces results superior to the combination of goserelin and tamoxifen for pre-menopausal women. Recently, the Austrian group conducted a randomised trial on adjuvant endocrine therapy in pre-menopausal women.[19] This large trial tested the effect of adding zoledronic acid to adjuvant endocrine treatment (goserelin plus tamoxifen or anastrozole). The results show that adding zoledronic acid to adjuvant endocrine therapy prolongs disease-free survival in these patients without adding substantially to the burden of adverse events. No difference has been demonstrated between goserelin plus tamoxifen or anastrozole. Nonetheless, as described in this study and our previously published study, we have clearly shown that high rate of CB with reasonably long duration when goserelin was used in combination with an AI, in both first-line and subsequent lines of treatment in pre-menopausal women with advanced breast cancer which remained hormone sensitive (sensitive to hormone therapy).[11] Whilst this is not the primary scope of this paper, megestrol acetate on its own has also been effective in these patients. A combination of goserelin and the pure anti-oestrogen fulvestrant has also been shown in a pilot study to work in pre-menopausal women with hormone sensitive advanced breast cancer – a CB rate of 45.5% was achieved when the combination was used as a first- to fourth-line endocrine therapy.[20] All these potentially extend the use of endocrine therapy in this group of patients.

Combined use of LHRH agonist plus AI extends the use of endocrine therapy in pre-menopausal advanced breast cancer patients who remain hormone sensitive.

Conflict of interest statement

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