PERGAMON

European Journal of Cancer 39 (2003) 861–869

European Journal of Cancer

www.ejconline.com

Review

The use of gonadotrophin-releasing hormone (GnRH) agonists in early and advanced breast cancer in pre- and perimenopausal women

J.F.R. Robertson*, R.W. Blamey

Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

Received 14 February 2002; received in revised form 17 October 2002; accepted 15 November 2002

Abstract

Gonadotrophin-releasing hormone (GnRH) agonists, in particular goserelin ('Zoladex'), are increasingly being used for the treatment of breast cancer in women with functioning ovaries. They act by downregulating pituitary GnRH receptors, thereby suppressing the release of luteinising hormone (LH) and follicle stimulating hormone (FSH), which, in turn, reduce the main source of oestradiol production in the ovaries. GnRH agonists have been shown to be as effective therapeutically as surgical ovarian ablation in pre- and perimenopausal women with advanced breast cancer. The combination of a GnRH agonist such as goserelin with the peripheral oestrogen antagonist, tamoxifen, may be used to produce 'combined oestrogen blockade'. In advanced breast cancer, this regimen prolongs progression-free survival and increases both the response rate and duration relative to the use of a GnRH agonist alone. In patients with early breast cancer, the addition of goserelin to 'standard treatment' (i.e. surgery ± tamoxifen, chemotherapy or radiotherapy) results in a significant benefit in recurrence-free survival and overall survival. This benefit was most apparent in patients with oestrogen receptor (ER) +ve tumours. Goserelin, when used either alone or in combination with tamoxifen as an adjuvant systemic therapy in women with ER +ve tumours, has been shown in clinical trials to produce recurrence-free survival rates equivalent to cytotoxic chemotherapy such as cyclophosphamide, methotrexate, 5-fluorouracil (CMF). Evidence suggests that at least part of the effect of adjuvant cytotoxic chemotherapy in premenopausal women is produced by ovarian ablation. Endocrine therapy with goserelin or goserelin plus tamoxifen should now be considered a treatment option in the management of premenopausal women with ER +ve early breast cancer.

Keywords: GnRH agonist; Goserelin; Tamoxifen; Adjuvant; Breast cancer; 'Zoladex'; Ovarian suppression; Castration

1. Introduction

More than 100 years ago, Beatson demonstrated that endocrine ablation by oophorectomy was accompanied by a regression of disease in a patient with advanced breast cancer [1]. He also understood that control of lactation in cows that had recently calved was mediated by the ovaries and not through the central nervous system; an early description of hormone action.

In the premenopausal woman, gonadotrophin-releasing hormone (GnRH) is released from the hypothalamus in a pulsatile fashion (pulses approximately every 90 min) under normal physiological conditions and is carried by the portal veins directly to the anterior pituitary gland where it binds to GnRH receptors, stimulating the release of luteinising hormone (LH) and follicle stimulating hormone (FSH) [2]. The occupied receptors form clusters and are taken up into the pituitary cells. These inactivated receptors are replaced by newly synthesised receptors on the cell surface, ready for the next pulse of GnRH. LH stimulates the ovaries to produce oestrogens, including oestradiol.

This process is responsible for producing up to 90% of circulating oestradiol, depending on the phase of the menstrual cycle; the remainder in premenopausal women, and all in postmenopausal women, is produced by aromatisation of androgens by the adrenal glands

* Corresponding author. Tel.: +44-115-962-7951; fax: +44-115-840-2618.

E-mail address: john.robertson@nottingham.ac.uk (J.F.R. Robertson).

0959-8049/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0959-8049(02)00810-9

and other tissues. Therapeutic approaches to the endocrine treatment of breast cancer have targeted both this regulatory pathway and the point of peripheral action of oestrogens by oestrogen receptor (ER) blockade.

Following Beatson's pioneering work, ovarian ablation by means of surgical castration, or later by irradiation, became a well-established means of endocrine manipulation in premenopausal women with advanced breast cancer. Response rates in metastatic breast cancer range from approximately 30% in unselected patients [3,4] up to 79% in patients with ER +ve tumours [5,6].

Surgical ablation is a relatively straightforward procedure with little perioperative morbidity, but it is an invasive method and has the potential of psychological upset, particularly in non-responders. An alternative to surgery is to use irradiation. Radiation ablation produces similar response rates to surgical ablation, but also has occasional long-term complications, takes longer to achieve castrate levels of oestradiol and long-term suppression is unreliable. Both procedures are irreversible and since only around one-third of patients may respond to this type of therapy, a sizeable proportion will have undergone these procedures for no clinical benefit.

The possibility of being able to suppress oestradiol levels medically is an attractive option. Use of GnRH agonists to downregulate GnRH production by the hypothalamus effectively produces a 'medical ablation' of the ovaries which is potentially reversible on discontinuation of therapy. Data showing the effectiveness of GnRH agonists in patients with advanced breast cancer were first published using buserelin [7], and goserelin ('Zoladex') [8]. Other members of this class include leuprorelin and triptorelin. Goserelin is the most extensively investigated member of the GnRH agonists, accounting for over 90% of the published data on GnRH agonists in the treatment of breast cancer, and no comparisons between the GnRH agonists have been reported.

During long-term administration, the GnRH receptors are effectively over-stimulated, resulting in down-regulation of the GnRH receptors in the pituitary gland. Experience over the last decade shows that goserelin provides an effective means of 'medical oophorectomy' for as long as the agent is administered. In the clinical setting, goserelin has been widely tested in early and advanced breast cancers. Ovarian suppression with goserelin has a more rapid onset than ovarian irradiation and its effects on ovarian function are reversible in most women [9], which may be important in premenopausal women in the adjuvant setting.

1.1. Pharmacodynamics of GnRH agonist therapy

The pharmacodynamics of goserelin in breast cancer were studied in the 1980s. The early work used daily subcutaneous (s.c.) injections [8], which were superseded by the monthly depot formulation of goserelin (3.6 mg) [8] that is now used in clinical practice. Goserelin produced an initial rise in LH and FSH for 7–10 days followed by a decrease in LH and FSH after 14–21 days in premenopausal women with advanced breast cancer. Progesterone and oestradiol levels followed those of the gonadotrophins with a short-lived rise followed by a fall to levels seen in oophorectomised or postmenopausal women 14–21 days after continuous administration. Similar endocrine responses were seen in women who received either daily (s.c.) injections or the monthly depot formulation of goserelin [8].

The ability of the monthly depot of goserelin to suppress serum concentrations of FSH, LH and oestradiol was also demonstrated in a study of 118 evaluable pre- and perimenopausal patients with metastatic breast cancer. This study showed that mean serum oestradiol values fell into the range seen in castrated or postmenopausal women (i.e. <30 pg/ml) after 2–3 weeks of treatment and suppression was maintained throughout therapy (up to 24 months) [10].

1.2. Effects of GnRH agonists on ovarian histology

While GnRH agonists suppress gonadotrophins and oestrogens to castrate levels in premenopausal women, leading to the cessation of menses, it is important to understand the effects of GnRH agonists on folliculogenesis and follicular maturation since these may indicate the potential for maintaining fertility following discontinuation of treatment.

The expectation was that goserelin would inhibit folliculogenesis by decreasing FSH and LH to very low levels. However, a study of ovarian histology showed that goserelin inhibits follicular maturation, but not folliculogenesis [11]. This is an important finding for young women with breast cancer as it may be expected that after discontinuation of goserelin, and the return of the pretreatment endocrine environment, maturation of the follicles will occur with a resumption of fertility. This would not be possible following surgical oophorectomy, irradiation or chemotherapeutic ablation.

1.3. Pharmacodynamics of GnRH agonists and tamoxifen in combination

An important question is whether there are any advantages to 'combined oestrogen blockade' using goserelin and tamoxifen in premenopausal women, gaining a double effect by first rendering the patient postmenopausal by the use of goserelin and then an additional effect from the use of tamoxifen, as in postmenopausal women.

In addition to the potentially greater antitumour effect, tamoxifen may theoretically shield the tumour

from the initial surge in oestradiol seen with goserelin monotherapy. In addition, goserelin has been shown to prevent the intermittent spikes of oestradiol seen with tamoxifen monotherapy [12]. Co-treatment with a GnRH agonist has been shown to prevent the formation of ovarian cysts when added to tamoxifen therapy [13].

The pharmacodynamics of goserelin in combination with tamoxifen have been compared with the effects of goserelin alone in pre- and perimenopausal women with advanced breast cancer. The initial surge in gonadotrophin levels with goserelin alone or in combination with tamoxifen lasted 7–10 days and was followed by a profound suppression of LH and FSH on both regimens. The combination had a more marked effect on serum FSH than goserelin alone [14] and the combination prevented the upward drift of FSH seen with goserelin alone. Both regimens suppressed serum oestradiol and progesterone to levels equivalent to those seen after surgical oophorectomy and there were no peaks in serum oestradiol with the combination.

2. GnRH agonists in advanced breast cancer

2.1. Clinical aspects of GnRH agonist monotherapy

The effectiveness of goserelin in the treatment of advanced breast cancer in pre- and perimenopausal women was established in a combined analysis of 29 phase II studies [15]. A total of 333 pre- and perimenopausal women with histologically-confirmed stage III or IV breast cancers was recruited between 1982 and 1988. Each patient received a goserelin depot injection every 28 days.

Of the 333 patients recruited, 228 patients were evaluable for efficacy. Treatment with goserelin gave a median survival of 26.5 months (range: 0.8–69 months); survival was longer in ER +ve patients (33.1 months) than in ER −ve patients (15.9 months) [16]. The objective clinical response rate was 36% (83/228 patients) and the subjective response rate was 68% (97/142 patients). The highest response rates were observed in patients with ER +ve tumours (objective response 44%, versus 31% for ER −ve patients). The median duration of response was 44 weeks (4–160 weeks). The reported response rate in ER −ve disease was higher than expected. There is no proven explanation for this result, but it may reflect a less strict attention to detail (for example in the collection of fresh tumour tissue) in the measurement of ER prevalent at that time.

The overall response rates were similar to those expected from surgical ablation in premenopausal women with advanced breast cancer. In a randomised trial of medical (GnRH agonist) versus surgical ovarian ablation, patients with ER and/or progesterone receptor (PgR) +ve tumours were assigned to receive goserelin depot ($n=69$) or surgical oophorectomy ($n=67$) [17]. The two treatment modalities were comparable in terms of objective clinical response (goserelin 31%; oophorectomy 27%) and stable disease (goserelin 28%; oophorectomy 26%). Overall and progression-free survival were similar for both goserelin and oophorectomy.

The endocrine and clinical data support the use of goserelin as a means of providing 'medical oophorectomy' in pre- and perimenopausal women with advanced breast cancer. Goserelin is well tolerated [15] and offers a non-invasive and reversible alternative to surgical ablation.

Data from other GnRH agonists have also demonstrated the efficacy of GnRH agonist monotherapy in premenopausal patients with advanced breast cancer. In several separate studies of leuprorelin, objective response rates of between 34 and 44% were reported [18–21]. Studies with buserelin monotherapy have reported objective response rates of 14–41% [22–25], while treatment with triptorelin has been shown to produce objective response rates of between 30 and 70% in premenopausal patients with advanced breast cancer [26–28].

2.2. Combination of GnRH agonists and tamoxifen in advanced breast cancer

A pilot study showed an overall response rate of 25% [29] with the combination of goserelin and tamoxifen in premenopausal women with advanced breast cancer.

Four randomised trials ([24,30,31] T. Tominaga, unpublished) have been undertaken to address whether combination therapy with a GnRH agonist and tamoxifen is superior to treatment with a GnRH agonist alone in pre- and perimenopausal patients with advanced breast cancer. Three of the studies used goserelin (79% of patients) and one used buserelin.

The study treatments compared initial combination therapy versus initial GnRH agonist alone: progression was assessed as the first progression after initiation of either therapy. In one of the studies, the largest of the four (ICI 2302) [31], the study was also designed to compare initial combination therapy with a sequential policy, where tamoxifen was added to goserelin when signs of progression were observed on goserelin monotherapy.

In the first of these trials, 85 perimenopausal patients with ER +ve metastatic breast cancer received ovarian ablation (surgery or irradiation), ovarian ablation plus tamoxifen, goserelin or goserelin plus tamoxifen. Objective response rates were 46% with ovarian ablation, 11% with ovarian ablation plus tamoxifen, 27% with goserelin and 45% with goserelin plus tamoxifen; differences between the treatments were not significant. There was no significant difference in the time to treatment progression (TTP) or time to death (TTD)

between the groups. The authors concluded that goserelin was of comparable efficacy to ovarian ablation by surgery or irradiation and that tamoxifen enhanced the efficacy of goserelin, but not ovarian ablation [30].

In a second study of 161 premenopausal patients with advanced breast cancer, combined treatment with buserelin plus tamoxifen was significantly superior to either treatment alone for both TTP and TTD. Time to progression was 9.7, 6.3 and 5.6 months for combined, buserelin and tamoxifen groups, respectively. There was no significant difference in the objectives response rates between treatments (48, 34 and 28%, for combined, buserelin and tamoxifen groups, respectively), but clinical benefit rates (including patients in whom their disease did not progress for > 6 months) were statistically greater for the combined treatment group (75%) compared with buserelin or tamoxifen alone (62 and 44%, respectively; $P = 0.007$) [24].

The third study compared the efficacy of goserelin alone and in combination with tamoxifen in 318 pre/perimenopausal patients with advanced breast cancer. In this study, objective response rates were comparable between treatments (31 and 38% in goserelin and goserelin plus tamoxifen groups, respectively). Although TTP was significantly greater with the combination treatment (23 weeks versus 28 weeks for goserelin alone; $P = 0.03$), there was no significant difference between the treatments for survival [31].

These trials have been combined in a meta-analysis [32]. At the time of analysis, approximately 70% of the patients had died. The meta-analysis reported that initial combination treatment led to a 22% lower risk of mortality ($P = 0.02$), and a 30% lower risk of disease progression ($P < 0.001$), than was seen with GnRH agonist monotherapy (Table 1). The objective clinical response rate was also significantly higher with combination therapy (39%) than with initial monotherapy (30%). The duration of response was almost twice as long with combination therapy (median: 19.4 months) as with GnRH agonist monotherapy (median: 11.3 months).

Although the side-effects of the combination were numerically greater in the ICI 2302 trial, this trial concluded that there were no additional safety issues associated without providing substantive data with the combination therapy [31].

The ICI 2302 trial (included in the meta-analysis) was the only trial which had intended to compare the effect of initiating treatment with the combination of goserelin plus tamoxifen versus the sequence of adding tamoxifen to goserelin on disease progression. In 50% of progressions this addition of tamoxifen did not occur because patients had rapidly progressing disease and alternative therapy was deemed appropriate [31]. Nevertheless, in the 71 patients who received subsequent treatment with tamoxifen after progression on goserelin, 18% had an objective response and 41% had stable disease, giving a total of 59% with clinical benefit. The median time to further progression in this patient group was 20 weeks. These data suggest that there may be no benefit of combined over sequential endocrine therapy as long as the second agent is given at recurrence.

In clinical practice, if patients have rapidly progressing disease, combined therapy gives the chance of an improved response and may offer psychological and quality-of-life advantages. An advantage to using the combination in all patients is that they have an unbroken disease-free period whereas with the sequence, although the overall length of response may be the same or longer, the patient has disease progression during this time.

However, combined therapy does use two treatment modalities simultaneously and may restrict the options available for second- or third-line treatments. Therefore, patients with relatively indolent disease, such as ER +ve bone metastases, may be considered for sequential therapy, since the clinician can expect, with some confidence, to have the opportunity to add tamoxifen sequentially on disease progression.

2.3. Combination of GnRH agonists and aromatase inhibitors in advanced breast cancer

The use of GnRH agonists in premenopausal women essentially renders them postmenopausal. This allows the use of agents, such as aromatase inhibitors (AIs), that are traditionally reserved for the treatment of

Table 1
Summary of meta-analysis results comparing GnRH agonist therapy with GnRH agonist + tamoxifen in women with advanced breast cancer

Endpoint	GnRH-A alone ($n = 256$)	GnRH-A + TAM ($n = 250$)	Hazard ratio/odds ratio (95% CI)	P value
Primary				
Median survival (years)	2.5	2.9	0.78 (95% CI 0.63–0.96)	0.02
Secondary				
Median progression-free survival (months)	5.4	8.7	0.70 (95% CI 0.58–0.85)	<0.001
Objective response (%)	29.7	38.8	0.67 (95% CI 0.46–0.96)	0.03
Number (%) responders	76 (30%)	97 (39%)	–	–
Median duration of response (months)	11.3	19.4	–	–

GnRH-A, GnRH agonist; TAM, tamoxifen; GnRH, gonadotrophin-releasing hormone; 95% CI, 95% Confidence Interval.

breast cancer in postmenopausal patients. Of note, combination treatment with goserelin and either vorozole or formestane has been shown to produce a more profound suppression of oestrogen levels than treatment with goserelin alone [33,34]. Similarly, in 16 premenopausal women with metastatic or locally advanced breast cancer previously treated with goserelin plus tamoxifen, substituting anastrozole for tamoxifen upon disease progression produced a 76% further reduction in the serum oestradiol level ($P < 0.05$) above that initially achieved with goserelin plus tamoxifen (89% reduction from pre-treatment levels; $P < 0.05$). Clinically, the combination of goserelin plus anastrozole resulted in clinical benefit in 12 (75%) patients, with a median duration of remission of > 17 months [35]. The combination of goserelin plus formestane has also been shown to produce responses in patients progressing after an initial response to goserelin alone [34]. These data suggest that using GnRH agonists to convert premenopausal patients to a postmenopausal state will increase the range of endocrine treatments available for premenopausal advanced breast cancer patients. In particular, the combination of GnRH agonists with AIs provides a valuable treatment option for those patients who have progressed on tamoxifen therapy.

3. GnRH agonists as adjuvant therapy for early breast cancer

The primary management of early breast cancer is surgical removal of the tumour by mastectomy or lumpectomy, ± radiotherapy. The choice of adjuvant systemic therapy for early breast cancer depends on the patient's prognosis, menopausal status and ER status. Tamoxifen is the established adjuvant treatment for postmenopausal women with hormone-sensitive early breast cancer. For premenopausal patients with hormone-sensitive disease, treatment options include chemotherapy, tamoxifen, ovarian ablation and combinations of these therapies.

The value of adjuvant ovarian ablation (by surgical oophorectomy or ovarian irradiation) in premenopausal women was clearly established by the Early Breast Cancer Clinical Trials Group (EBCCTG) in 1996 [36]. The overview demonstrated a highly significant improvement for these measures over controls in both recurrence-free survival and overall survival in women < 50 years of age. The magnitude of the effect of ovarian suppression demonstrated in patients unselected by ER status is similar to that produced by postoperative chemotherapy: benefit was seen irrespective of the nodal status at diagnosis. The response to ovarian suppression or oophorectomy is greater among patients who are ER +ve. Therefore, the results in patients unselected by ER status are likely to be an underestimate of the benefit of ovarian ablation in patients with ER +ve tumours.

Recently, the results of five comparative trials of adjuvant hormonal therapy using GnRH agonists alone [37,38] or in combination with tamoxifen [39–41], versus cytotoxic chemotherapy have shown at least equivalence of effect in premenopausal women with ER +ve tumours (see below).

3.1. Efficacy of GnRH agonists in adjuvant therapy

The Zoladex Early Breast Cancer Research Association (ZEBRA) trial compared six cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) with 2 years of treatment with goserelin in 1640 pre- and perimenopausal patients aged ⩽50 years with node +ve disease [37]. In the patients with ER +ve tumours (74%), goserelin was equivalent to CMF in terms of disease-free survival (DFS) at a median follow-up of 6 years (hazard ratio (HR) = 1.01; 95% confidence interval (CI) 0.84–1.20). In patients with ER −ve tumours, goserelin was inferior to CMF for DFS (HR = 1.76; 95% CI 1.27–2.44) (Fig. 1).

The Italian Breast Cancer Adjuvant Study Group (GROCTA) 02 trial ($n = 244$) [40,42] evaluated adjuvant treatment with CMF versus ovarian suppression (oophorectomy $n = 6$, irradiation $n = 31$, goserelin $n = 87$) plus tamoxifen in patients with ER +ve breast cancer. This trial showed that at a median follow-up of over 7 years, there were no differences with respect to either DFS or overall survival in patients treated with ovarian suppression plus tamoxifen compared with those treated with CMF. For tamoxifen plus ovarian suppression compared with CMF, the HR of relapse was 0.95 (95% CI 0.62–1.46; $P = 0.8$) and of death was 0.71 (95% CI 0.38–1.31; $P = 0.3$).

The Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial ($n = 1088$) [39] in women with ER +ve and/or PgR +ve tumours showed the combination of goserelin and tamoxifen to be more effective than CMF chemotherapy in terms of recurrence-free survival ($P < 0.02$) over a median follow-up of 50 months. Overall survival data are currently immature and show no statistical difference between the two treatment groups.

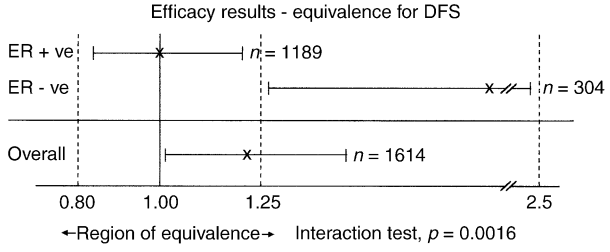

Fig. 1. Disease-free survival (DFS) by Oestrogen Receptor (ER) status in the Zoladex Early Breast Cancer Research Association (ZEBRA) trial.

A French study [41] compared triptorelin plus tamoxifen for 3 years with FEC (5-fluorouracil, epirubicin and cyclophosphamide) for six cycles in 333 premenopausal women with hormone receptor +ve disease. Overall survival and DFS over 54 months were similar in both arms ($P=0.18$, 0.12, respectively).

The Takeda Adjuvant Breast Cancer Study with Leuprorelin (Enantone) (TABLE) study [38] compared six cycles of CMF with 2 years of leuprorelin in 600 pre/perimenopausal patients: over 90% of patients in each group were hormone receptor +ve. Progression-free survival rates at 2 years were not significantly different between the two treatment arms (67.7% with hormone treatment and 63.1% with CMF).

Three other trials did not directly compare cytotoxic therapy with hormonal therapy, but are of interest.

The Zoladex In Premenopausal Patients (ZIPP) trial [43] determined the effect of adding goserelin to standard adjuvant treatment (surgery±radiotherapy ±chemotherapy±tamoxifen) compared with the effect of standard treatment alone in women <50 years of age. At a median follow-up of 66 months, the event-free survival was significantly longer for patients who received goserelin in addition to standard therapy compared with those who did not (HR=0.80; 95% CI 0.70–0.92; $P<0.001$). Overall survival was also significantly prolonged (HR=0.82; 95% CI: 0.67–0.99; $P=0.04$). Subgroup analysis suggested that goserelin had its greatest effect in patients with ER +ve tumours who did not receive chemotherapy, but none of the tests for interaction were significant [44].

A study by the Eastern Cooperative Oncology Group (ECOG)/South West Oncology Group (SWOG)/CALGB (Cancer and Leukaemia Group B) [45] in ER +ve patients compared the addition of goserelin with or without tamoxifen to CAF (cyclophosphamide, doxorubicin and 5-fluorouracil). At a median follow-up of 6.2 years, this study (INT-0101) showed a trend in favour of improved DFS for the addition of goserelin to CAF, although this just failed to reach statistical significance. The addition of goserelin plus tamoxifen to CAF chemotherapy resulted in a significant benefit in DFS over the use of CAF plus goserelin ($P<0.01$). The percentages of patients disease-free after 5 years for CAF alone, CAF plus goserelin and CAF plus goserelin and tamoxifen were 67, 70 and 77%, respectively. In this study, the addition of tamoxifen seemed to be more efficacious in those women with postmenopausal oestradiol (E_2) levels at the end of adjuvant CAF therapy, while goserelin was more beneficial in women with premenopausal oestradiol levels at the end of CAF therapy (data not shown). This trial looked at the addition of goserelin to cytotoxic chemotherapy, but did not evaluate the more interesting question of the advantage of the addition of cytotoxic therapy to goserelin therapy. This was addressed in the International Breast Cancer Study Group (IBCSG) Trial VIII.

The IBCSG Trial VIII was initially designed to compare six cycles of CMF with either 2 years goserelin, six cycles of CMF followed by 18 months goserelin or no treatment in premenopausal women with node −ve early breast cancer. Enrolment into the untreated arm was discontinued when other trials showed that adjuvant therapy improves survival in node −ve disease. Interim analysis of 200 patients from the four original arms confirmed the benefits of adjuvant therapy in this patient group; 5-year DFS of treated patients was significantly longer than for untreated controls (77% versus 60%; $P=0.02$) [46]. Recent data from this study show that in patients with ER +ve tumours, there was no significant difference between the treatment groups for 5-year DFS (goserelin 81%; CMF 81%; CMF plus goserelin 88%). Thus, the authors conclude that the value of adding chemotherapy to goserelin is questionable in patients with node −ve, hormone-sensitive disease [47].

In a small study ($n=92$) in premenopausal women with ER +ve disease, the addition of goserelin to epirubicin provided no statistically significant benefit in terms of overall survival or DFS in addition to that seen with chemotherapy alone [48].

3.2. Tolerability of GnRH agonists in adjuvant therapy

It is well established that chemotherapy is associated with toxicities such as: myelosuppression, gastrointestinal effects (anorexia, nausea, vomiting and diarrhoea), mucositis, stomatitis, alopecia and general fatigue. Treatment with GnRH agonists is associated with menopausal side-effects such as hot flushes and vaginal dryness. There are few data available directly comparing the tolerability profiles of these treatment modalities.

In the ZEBRA study, CMF was associated with more nausea/vomiting, alopecia and infection than goserelin, while goserelin initially produced more side-effects related to oestrogen suppression. Once adjuvant therapy had ceased, the incidence of menopausal side-effects was greater in women given cytotoxic chemotherapy than in those treated with goserelin. The increased incidence of menopausal side-effects in the chemotherapy group is associated with the high level of permanent amenorrhoea in this group (at 3 years 79% of patients treated with CMF were amenorrhoeic) [9].

Of note, overall quality of life was significantly better with goserelin in the first 3–6 months of the trial ($P<0.0001$) and did not differ significantly between treatments thereafter.

These results are supported by the TABLE study [38] in which serious adverse events were reported by 3.6% of those receiving hormonal therapy and 15.4% of those receiving cytotoxic chemotherapy.

In summary, these trials have shown that hormonal therapy with goserelin (±tamoxifen) is at least as effective as cytotoxic regimens in premenopausal women with ER +ve tumours, and is not associated with the distressing side-effects of chemotherapy. In addition, goserelin±tamoxifen can provide benefit when added to standard adjuvant therapy.

3.3. The role of amenorrhoea in women with ER +ve tumours treated with cytotoxic agents

Cytotoxic regimens render 20–80% of premenopausal women amenorrhoeic, depending on their age, the cytotoxic agent and cumulative dose used [9,49,50]. Since castration by any means has a powerful risk-reducing effect in the adjuvant setting [36], it follows that some of the effect seen with adjuvant chemotherapy is brought about by the side-effect of chemical castration.

Several studies have shown that amenorrhoea is a significant prognostic factor in premenopausal women with early breast cancer treated with chemotherapy: amenorrhoeic patients showed improved disease-free survival compared with those women who continued to menstruate [50–52]. In the Austrian study [50], 80% of patients receiving cytotoxic chemotherapy became amenorrhoeic and this subgroup of patients had significantly fewer recurrences and improved overall survival compared with the 20% who had continued menses through and after chemotherapy. In the ZEBRA trial, recurrence-free survival was superior in those treated with CMF who became amenorrhoeic compared with those who did not [37].

3.4. Prescription of adjuvant therapy for premenopausal ER +ve tumours

Adjuvant treatment should be tailored to need, i.e. prognosis. There are alternative strategies for classifying patients into low, moderate and high risk (such as the Nottingham Prognostic Index [53], which we favour). A group of patients with a good prognosis can be identified, in whom the potential absolute benefit of adjuvant therapy is very small and adjuvant therapy is not indicated.

In those patients with ER +ve tumours and moderate prognoses, the authors believe that the risk–benefit analysis favours adjuvant hormone therapy alone, although clearly this should be discussed with each individual patient. In the remaining patients with poor prognoses, a considerable absolute gain can be expected from hormonal therapy, but given the high percentage of recurrences, there is probably a further absolute gain from the application of cytotoxic chemotherapy and the authors would advise chemo-endocrine therapy in these patients.

This tailored approach highlights the difference between basing treatment on relative risk for all versus absolute risk for an individual patient.

4. Conclusions

The use of GnRH agonists such as goserelin is as effective as surgical oophorectomy or radiotherapeutic ovarian ablation in the management of premenopausal women with ER +ve advanced breast cancer and provides a non-invasive, reversible method of ovarian suppression. In early breast cancer, GnRH agonists have been shown to be as effective as CMF chemotherapy in hormone-sensitive disease.

The combination of a GnRH agonist with tamoxifen as first-line therapy for advanced disease can be used to improve the initial response rate and considerably lengthen the duration of response. In early disease, goserelin plus tamoxifen has been shown to be more effective that CMF chemotherapy.

Current treatment guidelines from St Gallen and the European Society of Mastology (EUSOMA) now recommend the use of a GnRH agonist±tamoxifen as treatment for premenopausal women with hormone-sensitive early breast cancer.

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