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Focus On

New opportunities in premenopausal breast cancer: goserelin ('Zoladex') plus aromatase inhibition

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Abstract Results from trials demonstrating the superiority of the third-generation aromatase inhibitors (AIs; anastrozole, letrozole and exemestane) vs. tamoxifen have led to changes in clinical practice in the treatment of postmenopausal patients with hormone-sensitive breast cancer. AIs do not inhibit ovarian oestrogen synthesis sufficiently to be a viable monotherapy for premenopausal patients but there is interest in their potential use in combination with luteinising hormone-releasing hormone analogues (LHRHas) such as goserelin ('Zoladex'). Preliminary results from Phase II combination trials in the advanced breast cancer setting have been promising, but efficacy data in premenopausal patients with early disease are yet to be reported. Here we overview the rationale and preliminary results to date for the combination of AIs with an LHRHa and highlight ongoing trials that will more fully assess the value of such combinations in extending the treatment options for premenopausal breast cancer patients.

Keywords: Aromatase inhibitor; Breast cancer; Goserelin; Premenopausal

Introduction

Patients with hormone receptor-positive breast cancer are candidates for endocrine therapy, which works by blocking the growth-promoting action of oestrogen on the tumour. Endocrine agents either block the action of oestrogen at the oestrogen receptor (ER; e.g. tamoxifen or fulvestrant) or abrogate oestrogen production (ovarian ablation or aromatase inhibitors; AIs). As the ovaries are the primary source of oestrogen in premenopausal women, ovarian ablation is an effective way of radically reducing oestrogen levels in these patients. In contrast to their efficacy in postmenopausal women, whose primary source of oestrogen is the aromatisation of androgens in peripheral tissues, the AIs do not reduce oestrogen levels sufficiently to be effective as monotherapy in premenopausal women.

Ovarian oestrogen production in premenopausal breast cancer patients can be irreversibly ablated with either oophorectomy or ovarian irradiation. Potentially reversible medical ovarian ablation can also be achieved with a luteinising hormone-releasing hormone analogue (LHRHa) such as goserelin ('Zoladex'). Such treatment temporarily produces oestrogen levels in the postmenopausal range. Clinical trials have shown that combining an LHRHa with the selective ER modulator tamoxifen confers better efficacy compared with either agent alone in premenopausal patients with advanced breast cancer (ABC) [1,2]. In one study, the combination of an LHRHa plus tamoxifen was associated with significantly increased survival compared with an LHRHa or tamoxifen alone [1]. Progression-free survival was 9.7 months vs. 6.3 months and 5.6 months, respectively, and overall survival was 3.7 years vs. 2.5 years and 2.9 years [1]. Similarly, a meta-analysis of four randomised trials demonstrated significantly increased progression-free

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survival (8.7 months vs. 5.4 months) and overall survival (2.9 years vs. 2.5 years) for an LHRHa plus tamoxifen vs. an LHRHa alone [2].

Although no direct comparisons are available of goserelin alone vs. goserelin plus tamoxifen in the adjuvant setting, goserelin monotherapy has been shown to be of equivalent efficacy to cyclophosphamide/methotrexate/5-fluorouracil (CMF) in ER-positive patients [3] while goserelin plus tamoxifen is significantly superior in terms of relapse-free survival [4]. In a further study, there was no significant difference between goserelin and CMF in patients with ER-positive disease [5]. Moreover, following standard cyclophosphamide, doxorubicin, 5-fluorouracil (CAF) chemotherapy, goserelin plus tamoxifen was associated with improved disease-free survival compared with goserelin alone. This benefit was most apparent in women aged less than 39 years, those who did not become amenorrhoeic or who had premenopausal oestradiol levels after CAF [6].

In the postmenopausal setting, tamoxifen is now being superseded by the third-generation AIs (anastrozole, letrozole and exemestane) in the first-line treatment of ABC [7–9]. Similar changes in clinical practice are occurring in the treatment of early breast cancer with trials supporting the use of AIs as primary adjuvant treatments ahead of tamoxifen [10] and supporting the switching of patients already receiving tamoxifen to an AI [11–14]. These results suggest that it is worth investigating the potential of AIs in young women with breast cancer who are rendered menopausal by LHRHa treatment, to determine whether the same benefits that have been observed in postmenopausal women can be translated to the premenopausal setting.

Evidence supporting treatment with goserelin plus an AI

Endocrine effects

In postmenopausal women, the third-generation AIs (anastrozole, letrozole or exemestane) suppress plasma oestrogen levels by 80–90% compared with baseline values [15]. In premenopausal women, once plasma oestrogen levels have been inhibited to postmenopausal levels using an LHRHa, similar endocrine effects have been observed on the addition of an AI. In one small study in pre/perimenopausal patients with ABC, the combination of goserelin plus formestane produced similar oestrogen levels to those observed in postmenopausal women treated with formestane alone [16,17]. Dowsett and colleagues also compared treatment with goserelin plus vorozole in premenopausal women with vorozole alone in postmenopausal women. Although oestrogen levels were suppressed to a greater extent in postmenopausal women, addition of vorozole to goserelin resulted in greater oestrogen suppression than goserelin alone in the premenopausal group [18].

Limited data are also available on the endocrine effects of goserelin in combination with the third-generation AIs. The effects of goserelin plus anastrozole vs. goserelin alone have been examined in two Phase II studies in premenopausal women, one in patients with endometriosis [19] and one in patients with breast cancer [20]. In the first study, plasma oestrogen levels were significantly lower in patients receiving combination treatment, being approximately half those observed in patients receiving goserelin alone throughout the 6-month treatment period [19]. In the second study, 16 premenopausal patients with ABC were treated with goserelin plus anastrozole after previous treatment with goserelin plus tamoxifen (switched to anastrozole on disease progression). Goserelin plus tamoxifen resulted in an 89% reduction in mean oestradiol levels (pre-treatment vs. 6-month treatment: 224 pmol/l vs. 24 pmol/l; $P < 0.0001$). Substitution of tamoxifen with anastrozole on progression resulted in a further 76% fall (to 6 pmol/l at 3 months; $P < 0.0001$) [20] (Fig. 1). In a further non-comparative study goserelin plus anastrozole was found to effectively suppress serum oestradiol levels after 1 month of treatment (median baseline level: 47 pg/ml (range: <10–167 pg/ml); median level after 1 month: <10 pg/ml (range: <10–52 pg/ml)) [21]. Oestradiol levels in patients treated with goserelin plus anastrozole appear similar to those seen in postmenopausal women receiving an AI alone.

Efficacy data

Preliminary efficacy data for goserelin plus an AI are encouraging but so far have been limited to

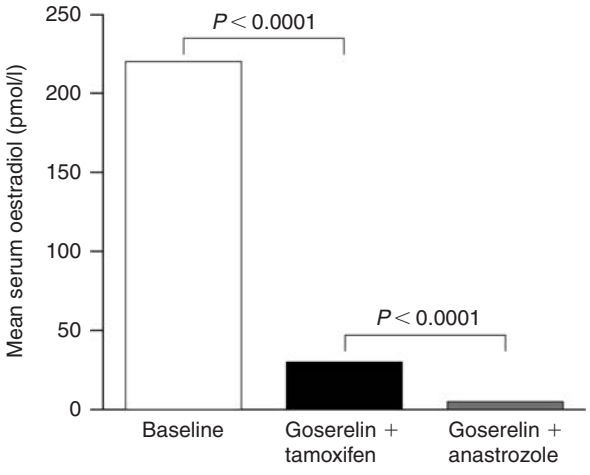

Figure 1.
Effect of 6 months of treatment with goserelin plus tamoxifen or goserelin plus anastrozole on serum oestradiol levels [20].

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premenopausal patients with ABC. Two of the Phase II studies that examined the endocrine effects of goserelin in combination with an AI have also reported efficacy data for this combination. In one of these studies, Dowsett and colleagues investigated the activity of goserelin plus formestane in six pre/perimenopausal women with ABC who had previously gained clinical benefit from goserelin monotherapy (switched to goserelin plus formestane at disease progression). They reported that four of the six patients experienced an objective response with combination treatment [16,17]. The second study included 16 patients with ABC (14 of whom had ER-positive disease) who had previously gained clinical benefit from goserelin plus tamoxifen. These investigators reported a 75% clinical benefit rate with the goserelin plus anastrozole combination and a median duration of response greater than 17 months [20]. Preliminary results of an ongoing Phase II study of goserelin plus anastrozole in premenopausal patients with hormone receptor (ER and/or progesterone receptor)-positive ABC were reported at the 2004 San Antonio Breast Cancer Symposium. At the time of analysis, 18 of the 30 planned patients were evaluable for assessment of response. Five of these 18 patients (28%) experienced an objective response (one complete and four partial responses) and eight (44%) had stable disease in excess of 6 months resulting in a clinical benefit rate of 72% [21].

Managing adverse bone effects

The tolerability profile of goserelin plus an AI is generally consistent with the expected effects of oestrogen withdrawal. However, one concern with using complete oestrogen blockade in premenopausal women is its detrimental effect on bone mineral density (BMD), which is a particular concern in patients receiving long-term adjuvant treatment. An ongoing randomised trial has shown that goserelin plus anastrozole is associated with greater bone loss than goserelin plus tamoxifen (mean loss −16% vs. −8%, respectively). However, the same study demonstrated that bone loss in both groups could be overcome by co-administration of zoledronic acid [22]. It seems reasonable to suggest that premenopausal women undergoing complete oestrogen blockade treatment should be managed in the same way as postmenopausal women receiving AIs. This would mean screening such patients for osteoporosis risk factors and advising them, where possible, to stop smoking, to moderate their caffeine and alcohol intake, to perform regular weight-bearing exercise, and to supplement their diets with appropriate amounts of calcium (to achieve 1500 mg daily intake) and vitamin D (400–800 IUs daily).

Summary and future directions

The combination of goserelin with an AI is an interesting prospect and, based on data in postmenopausal women, is the logical next step in the endocrine treatment of premenopausal women with hormone receptor-positive breast cancer. Current guidelines are increasingly recognising the potential for this combination [23,24]. Indeed, the National Comprehensive Cancer Network (NCCN) guidelines for advanced disease indicate that premenopausal women should be treated with ovarian suppression plus additional endocrine therapy in the same way as postmenopausal women are treated [24]. Consequently, ovarian suppression opens up therapy options for premenopausal women that would not otherwise be available.

Several large adjuvant trials in premenopausal patients are currently evaluating the efficacy and tolerability of ovarian suppression in combination with an AI. Two trials are specifically looking at goserelin plus anastrozole in this setting. Austrian Breast and Colorectal Cancer Study Group (ABCSG) 12 is a four-arm trial, which in addition to comparing the efficacy and tolerability of goserelin plus anastrozole with goserelin plus tamoxifen, is also assessing any potential benefits of adding zoledronic acid to these combinations. Although this trial is yet to report efficacy data, preliminary results from the pre-planned BMD sub-protocol have recently been reported [22]. A trial from the National Dutch Breast Cancer Trialists' Group is comparing the efficacy and tolerability of goserelin plus anastrozole (±radiotherapy) with goserelin plus anastrozole (±radiotherapy) in combination with 5-fluorouracil/epirubicin/cyclophosphamide (FEC) (The PROMISE trial).

Further trials of ovarian function suppression (OFS; using triptorelin, oophorectomy or ovarian irradiation) in combination with another third-generation AI, exemestane, are also ongoing. These include the Suppression of Ovarian Function Trial (SOFT) comparing OFS plus tamoxifen (±chemotherapy) vs. OFS plus exemestane (±chemotherapy) and the Tamoxifen and EXemestane Trial (TEXT) comparing OFS plus tamoxifen (±chemotherapy) vs. OFS plus exemestane (±chemotherapy). The Premenopausal Endocrine Responsive CHEmotherapy (PERCHE) trial is a more complex four-arm trial comparing OFS plus tamoxifen vs. OFS plus exemestane vs. OFS plus chemotherapy plus tamoxifen vs. OFS plus chemotherapy plus exemestane.

Such new directions in the use of LHRHas, most commonly goserelin, are offering fresh and exciting opportunities in the treatment of premenopausal breast cancer. Results from these ongoing trials are awaited with interest.

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