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Editorial Comment

Combining luteinising hormone releasing hormone agonists and aromatase inhibitors in breast cancer

*Jonathan Krell, Edwina K. Ewart, Justin Stebbing**

Department of Medical Oncology, Imperial College Healthcare NHS Trust, Imperial College, Charing Cross Hospital, Fulham Palace Road, London, W6 8RF, UK

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Except for those individuals with significant visceral disease, current guidelines tend to recommend endocrine therapy rather than chemotherapy as first-line treatment of metastatic breast cancer.[1] For the most part, aromatase inhibitors (AIs) have superseded tamoxifen as the treatment of choice in postmenopausal women with advanced breast cancer, and also as an adjuvant systemic therapy for early disease in postmenopausal women with ER positive tumours. Combined analysis of two international randomised, double-blind trials ($n = 1021$) demonstrated that in patients with ER/PgR+ tumours, first-line treatment with anastrozole significantly prolonged the time to progression (median TTP: 10.7 versus 6.4 months, respectively; $p = 0.022$) and response rate (29.0% versus 27.1%) compared with tamoxifen.[2] An EORTC trial also showed superiority of exemestane over tamoxifen as first-line hormonal therapy in terms of overall response rate and early progression-free survival[3] and a multinational randomised trial of letrozole versus tamoxifen, showed letrozole was associated with superior time to progression, overall objective response rate and overall survival in the first 2 years of treatment.[4]

Data regarding fulvestrant are now also maturing: in a randomised comparison in postmenopausal women who had progressed on adjuvant tamoxifen, there were no statistically significant differences in TTP or response rates between fulvestrant and exemestane.[5] Results from another trial, the FIRST study, demonstrated that first-line fulvestrant was at least as effective as anastrozole in terms of clinical benefit rate and overall response rate and was associated with a significantly longer time to progression in postmenopausal women with advanced hormone receptor–positive breast cancer.[6] However, for premenopausal women with metastatic ER^+ disease, AIs or fulvestrant can only be used in patients who have undergone ovarian suppression or ablation. Luteinising hormone releasing hormone (LHRH) agonists (e.g. goserelin) have been shown to produce effective ovarian function suppression in a similar manner to surgical oophorectomy or ovarian irradiation.[7] Trials have now confirmed the effectiveness of an LHRH agonist in combination with tamoxifen, in both advanced and adjuvant settings for premenopausal women with ER positive breast cancer[8,9] However, in the metastatic setting, there are no randomised data to demonstrate whether goserelin plus an AI confers superiority or non-inferiority to the combination of goserelin and tamoxifen in premenopausal women. Instead, there are now data from three studies showing efficacy of combining an LHRH agonist with an AI in this patient group; the mechanistic synergy of rendering individuals functionally postmenopausal using an LHRH agonist coupled with an AI is easy to appreciate.

* *Corresponding author:* Address: Imperial College Healthcare NHS Trust, Charing Cross Hospital, 1st Floor, E Wing, Fulham Palace Road, London, W6 8RF, UK. Tel.: +44 203 311 8295; fax: +44 208 846 1433.
E-mail address: j.stebbing@imperial.ac.uk (J. Stebbing).
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The first study was a prospective, single-arm, multicenter phase II trial involving 35 (32 evaluable) premenopausal individuals with ER^+/PgR^+, metastatic or recurrent breast cancer.[10] This demonstrated a 72% clinical benefit rate (3.1% complete response, 34.4% partial response and 34.4% stable disease) with a median time to progression of 8.3 months. The most common adverse events were fatigue (50%), arthralgias (53%), and hot flashes (59%). The second report is from a multi-centre study in France involving 33 patients with a clinical benefit rate of 63.6% and TTP of 13 months.[11]

The third study to report on the use of goserelin plus an AI in premenopausal women with advanced breast cancer is presented in this issue of the European Journal of Cancer by Cheung et al. Here, 36 premenopausal patients with metastatic hormone receptor positive breast cancer from a single institution were treated with goserelin plus anastrazole as first-line therapy. Within this, they report on a further 13 individuals who subsequently received goserelin plus exemestane as a later line of treatment, having previously had goserelin plus anastrozole. This 'AI switch' strategy makes this the first report on the continued use of goserelin to enable further use of another AI, in this case a non-steroidal (anastrazole) to a steroidal (exemestane) AI. Serial measurements of estradiol, androgens, and FSH and LH were also undertaken. Out of the 36 patients treated with goserelin plus anastrozole as first-line therapy, 24 (67%) achieved a clinical benefit at 6 months. The overall median duration of treatment measured >18 months (range 2–78 months) and the median TTP was 12 months (range 2–47 months). The treatment was well tolerated with no patients withdrawing due to adverse events. Out of the 13 patients who received goserelin plus exemestane as further therapy, five patients derived some benefit.

The combination of goserelin plus anastrazole resulted in 98% reduction (from pre-treatment to 6-month) in median levels of oestradiol while the levels of other hormones had minimal fluctuations during therapy. No further significant fluctuation in hormone levels were seen in those patients who progressed on goserelin plus anastrozole and switched to goserelin plus exemestane. Interestingly those who received megestrol acetate at some stage during their treatment sequence had a further reduction in testosterone and DHEAS levels and also a slight surge of FSH and LH levels during that treatment phase.

The authors have conducted an important study that demonstrates the combination of goserelin plus an AI produces sustained clinical benefit and minimal side-effects in many premenopausal women with ER^+ advanced breast cancer, in line with the two previous studies in this setting. This study is unique in reporting the use of an LHRH with sequential AI therapy, a practice that is surprisingly under-reported although used clinically in many institutions. Interestingly the combination of goserelin with an AI is sometimes used in the adjuvant setting, in those 'intolerant' to tamoxifen, without much supportive evidence. Cheung et al.'s study is also the first to report serial measurements of estradiol, androgens, and FSH and LH in this patient cohort although the patient numbers are limited.

Within the sample size limitations of such a study these data appear to support the use of goserelin plus AIs in hormone sensitive advanced breast cancer. The main toxicity of note observed across these studies is arthralgias,[12] and as individuals with hormone sensitive metastatic breast cancer may now have prolonged survivals it is probably worthwhile to also monitor bone density. Randomised studies as opposed to single-arm trials, comparing the use of first-line goserelin plus tamoxifen with goserelin plus AIs or fulvestrant may also help us understand the most effective sequencing of these agents in premenopausal women with hormone sensitive advanced breast cancer. In view of the recent decision of the US Food and Drug Administration to withdraw the label for bevacizumab in breast cancer, a trial comparing goserlin plus an AI versus paclitaxel and bevacizumab, or versus a taxane alone, in first-line therapy would be of enormous interest in hormone sensitive metastatic disease.

Conflict of interest statement

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