USE OF LUTEINISING HORMONE-RELEASING HORMONE AGONISTS FOR ADJUVANT TREATMENT OF EARLY BREAST CANCER

In 2003, the National Breast Cancer Centre commissioned a systematic review to clarify the role of LHRH agonists in pre-menopausal women with early breast cancer with a view to providing evidence to support the information needs of clinicians and policy makers. To access the full review click on the following link www.nbcc.org.au/bestpractice/treatment/index.html

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Review period: May–November 2003

The aim of adjuvant therapy in breast cancer is to prevent systemic recurrence and improve overall survival. Options for adjuvant therapy in women with breast cancer include radiotherapy, cytotoxic chemotherapy, ovarian ablation (with surgery or radiotherapy), ovarian suppression (with luteinising hormone-releasing hormone (LHRH) agonists) and anti-oestrogen therapy.

What are LHRH agonists?

LHRH agonists (goserelin, leuprorelin, buserelin nafarelin and triptorelin) down-regulate the LHRH receptors in the pituitary gland, thereby suppressing luteinising hormone and oestradiol. These agents provide effective ovarian suppression in pre-menopausal women. In contrast to ovarian ablation by surgery or radiotherapy, LHRH agonists induce a menopausal status that is reversible on cessation of treatment.¹

Current use of LHRH agonists

LHRH agonists have been shown to be an acceptable alternative to ovarian ablation by surgery or radiotherapy.² The benefits of LHRH agonists in the treatment of pre-menopausal women with hormone-sensitive advanced breast cancer have been demonstrated.³
In Australia, use of goserelin is authorised by the Therapeutic Goods Administration (TGA) for ‘treatment of pre-menopausal women with hormone-dependent advanced breast cancer’. Goserelin is the only LHRH agonist approved for the treatment of breast cancer in Australia. Its use is not subsidised by the Pharmaceutical Benefits Scheme (PBS).

**Systematic review results**

The methodology, search criteria and quality appraisal methods for the systematic review are outlined in the full report. The review focused on properly controlled randomised trials comparing LHRH agonists to tamoxifen (TAM), cyclophosphamide, methotrexate, 5-fluorouracil (CMF), and other chemotherapy regimens. Because of the lack of efficacy of hormonal therapy in oestrogen receptor negative (ER–) women demonstrated in previous trials, the review was limited to women with oestrogen receptor positive (ER+) disease.

Eleven randomised trials were identified and summarised. Information was available as a conference abstract for six trials3–8 and as a full journal article for five trials.9–13 These trials included a total of 10,022 women. The trials investigated goserelin,3,4,5,7,9,11–13 leuprorelin,10 buserelin8 and triptorelin.6 These LHRH agonists were used for varying time periods, most commonly two to three years. In one trial, goserelin was used and well tolerated for five years4 but further trials are needed to address treatment duration.

*Comparison with tamoxifen*3,13

Data are currently inadequate to inform conclusions about the relative efficacy of LHRH agonists compared with TAM.

*Comparison with CMF chemotherapy*5,9,10

In three trials of pre-menopausal women with early breast cancer, adjuvant suppression of ovarian function using goserelin or leuprolelin, with or without TAM, had similar benefits to adjuvant CMF chemotherapy in terms of disease-free survival (DFS) and overall survival (OS) at two to six years follow-up.
Comparison of combined hormonal therapy (LHRH agonist + tamoxifen) with chemotherapy\textsuperscript{6,11,12}

Trial results suggest that combined hormonal therapy is equivalent in efficacy to non-anthracycline and sub-optimal anthracycline chemotherapy.

- Two trials demonstrated equivalent efficacy for combined hormonal therapy compared with non-anthracycline chemotherapy,\textsuperscript{11,12} with one trial showing a significant advantage to goserelin and TAM over CMF in terms of recurrence free survival at a median follow-up of five years (81% vs 76%, \( p=0.037 \)).\textsuperscript{12}

- One study showed that combined hormonal therapy was equivalent to anthracycline chemotherapy, although the dose of epirubicin used in this study has since been shown to be sub-optimal.\textsuperscript{6}

Combination hormonal therapy and chemotherapy\textsuperscript{3–5,7,8}

No benefit from the addition of CMF to an LHRH agonist has been demonstrated\textsuperscript{5} and no benefit from the addition of an LHRH agonist to adjuvant CMF or cyclophosphamide, doxorubicin, 5-flurouracil (CAF) has been demonstrated.\textsuperscript{3–5} Furthermore, no conclusive benefit from the addition of combined hormonal therapy (LHRH + TAM) to adjuvant chemotherapy with CMF, CAF or doxorubicin has been demonstrated.\textsuperscript{3,7,8}

Comparison with ovarian ablation by surgery or radiotherapy

No trials were identified that compared LHRH agonist-induced ovarian suppression with ovarian ablation by surgery or radiotherapy. Extrapolating from trials performed in advanced breast cancer, it could be hypothesised that both surgical ablation of the ovaries and ovarian suppression using LHRH agonists would have similar benefits in terms of disease-free survival and overall survival. However, the side effects of treatment may differ. The complications of early menopause induced by treatment, including accelerated bone loss, vascular disease and infertility, are likely to be influenced by the age distribution of the women receiving treatment. Younger women will experience a longer duration of additional menopause than women closer to the age of natural menopause at treatment. As surgical ablation is permanent, compared with the reversible ovarian suppression seen with LHRH agonists, women undergoing surgical ablation are more likely to experience these complications.
Toxicity and quality of life

The main side effects reported with LHRH agonists were:

- menopausal symptoms\textsuperscript{2,14,15} – symptoms improved on cessation of LHRH agonist treatment while persisting in patients receiving cytotoxic chemotherapy

- vasomotor symptoms – patients receiving goserelin alone or in combination with TAM reported more vasomotor symptoms than patients receiving TAM alone\textsuperscript{14,15}

One study that assessed quality of life demonstrated significantly better scores for physical symptoms, activity level and ability to cope with illness during the first three to six months of treatment for women receiving goserelin compared with those receiving CMF (p<0.00001)\textsuperscript{9,16}. After six months, there was no significant difference between the two groups. The positive change from baseline in overall quality of life score was significantly greater in the goserelin group during the first three to six months (p<0.00001), while at one, two and three years there was no difference.

Conclusions

This review indicates that LHRH agonists are well tolerated and have a different side-effect profile to that of TAM or chemotherapy. The findings suggest that ovarian suppression using LHRH agonists is a reasonable alternative to TAM or CMF chemotherapy in women with ER+ early breast cancer who have a contradiction or intolerance to these standard therapies. Whilst there are no trials comparing LHRH agonists with ovarian ablation via radiotherapy or surgery, they appear to be an effective alternative for women with early breast cancer.

The role of chemotherapy in addition to LHRH agonists is not clearly defined and mature results of four trials are awaited\textsuperscript{3–5,7}. Data are also inadequate at the time of publication to inform decisions about the efficacy of LHRH agonists in comparison with TAM for the treatment of ER+ early breast cancer.

A major limitation of the trials reviewed is that they all used control arms that are no longer considered standard and therefore the applicability of these results to current clinical practice is cautioned. Individual trial numbers are small. A meta-analysis of the data once trials have matured may help to delineate the role of LHRH agonists, although variability in both entry criteria of each trial and the treatment given may make this difficult.
The conclusions of this systematic review are based on evidence available to November 2003. New data are constantly emerging. The conclusions of this systematic review are likely to change with longer follow-up periods and in light of evidence from other trials.
References


6. Roche H, Kerbrat P, Bonneterre J et al. Complete hormonal blockade versus chemotherapy in pre-menopausal early-stage breast cancer patients (pts) with positive hormone-receptor (HR+) and 1–3 node-positive (N+) tumor: results of the FASG 06 trial. *Proc ASCO* 2000;(abstr 279).


