

## RESEARCH ARTICLE

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# Clinical Studies Investigating the Use of Leuporelin in Breast Cancer Patients from Asia

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### Abstract

Leuporelin is a synthetic analogue of naturally occurring gonadotropin-releasing hormone. It is currently approved in the United States, Europe and Asia and has indications in advanced prostate cancer, endometriosis, breast cancer and precocious puberty. This review examined clinical trials of leuporelin in women with breast cancer in Asia. **Methods:** Four studies were identified, involving 999 premenopausal females with breast cancer. Leuporelin was administered subcutaneously at doses of 3.75 mg every 4 weeks, 11.25 mg every 12 weeks or 22.5 mg every 24 weeks in addition to either adjuvant chemotherapy or hormonal therapy. **Results:** Leuporelin was shown to preserve ovarian function, reduce symptoms of ovarian failure, the occurrence of early menopause, and the time to resumption of menses. Leuporelin-related adverse events included hot flush, mood swings and urogenital symptoms. **Conclusion:** Clinical studies in breast cancer patients from Asia have primarily investigated the effect of leuporelin on the protection of ovarian function in patients who receive chemotherapy, assessed the ability of leuporelin to suppress serum estradiol to menopausal levels, or to determine the efficacy and safety of leuporelin in daily medical practice.

**Keywords:** Breast neoplasms- menopause- premenopause- leuprolide- fertility

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### Introduction

The incidence of breast cancer is about 10% for most regions of the world, (Asthana et al., 2014) and appears to be increasing in Asian regions (Ataya et al., 1995; ClinicalTrials.gov, 2017). Increases in incidence may reflect better screening and detection. Despite mortality from breast cancer decreasing in some regions in Asia, 6 others have reported an increase in mortality, Ataya et al., (1995) suggesting that treatment may not be optimal in some regions.

Approximately 15% of breast cancers are diagnosed in patients of reproductive age (GLOBOCAN, 2016). Unfortunately, treatment with adjuvant systemic chemotherapy, particularly cyclophosphamide based therapy, while offering the promise of improved survival, comes at the cost of premature ovarian failure (GLOBOCAN, 2016). Leuporelin is a synthetic analogue of naturally occurring gonadotropin-releasing hormone (GnRH), which acts as a potent inhibitor of pituitary gonadotropin secretion when given continuously at therapeutic doses. Leuporelin is approved for the treatment of hormone-dependent diseases, including advanced prostate cancer, endometriosis, breast cancer and precocious puberty. In humans, administration of

leuporelin results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol [E2] in premenopausal females). However, continuous administration of leuporelin results in decreased levels of LH and FSH, usually within 2 to 4 weeks from initiation of treatment. Cessation of GnRH leads to resumption of normal ovarian function. Leuporelin has been used to protect the ovaries against chemotherapy-induced toxicity (Kim et al., 2014; Kurebayashi et al., 2017).

### Materials and Methods

Leuporelin is approved for the treatment of hormone-dependent diseases, including advanced prostate cancer, endometriosis, breast cancer and precocious puberty. It is currently approved for use in the United States, Europe and Asia, and can be administered every 4, 12 or 24 weeks, although approved formulations and indications vary.

In September 2015, leuporelin 22.5 mg subcutaneous injection became the world's first product to obtain approval for the treatment of premenopausal breast cancer

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as a 24-week depot, it gained approval in Japan following the results of two Phase III, multicenter, randomized, open-label clinical studies (Lambertini et al., 2015; Park et al., 2010).

The purpose of this review is to examine how leuprorelin is being investigated for the treatment of patients with breast cancer in Asia and to investigate outcomes experienced by these patients following treatment with leuprorelin. Searches were conducted in PubMed, the Cochrane library and clinicaltrials.gov. Articles were included if they were published in English between 1 January 2000 and 31 December 2016. Eligible studies were Phase I-IV and included Asian women with breast cancer who had been treated with leuprorelin. Study eligibility assessment was performed in a manual, non-blinded manner by a single person. Studies retrieved using the search criteria with an abstract available for review were screened against the eligibility criteria described above. Studies with no abstract to review and congress abstracts were excluded. Studies were also excluded if their abstract did not mention 'leuprolide' and 'breast cancer', or one of their associated MeSH Entry Terms (UK or US spelling). Finally, full-text articles of the remaining studies were screened against the remaining eligibility criteria and included in the final analysis if they were still eligible.

Regarding the requirement for studies including participants from Asia, studies were only included if they reported data from countries within Southeastern Asia, Far East Asia, or Western Asia excluding the Middle East; the PubMed MeSH Term for Asia was referred to for country categorization.

## Results

Of 55 identified studies, four studies were included, involving 999 analyzed patients. All participants were premenopausal females with a prior diagnosis of breast cancer (Table 1). Exclusion criteria in relation to prior chemotherapy or hormonal therapy varied between the studies (GLOBOCAN, 2016; Lambertini et al., 2015; Recchia et al., 2015). Leuprorelin was administered as a subcutaneous injection in each of the four studies, and was administered at 3.75 mg every 4 weeks, 11.25 mg every 12 weeks, or 22.5 mg every 24 weeks. In each study, leuprorelin was administered with either adjuvant chemotherapy or hormonal therapy. Only one study had a comparator arm, in which leuprorelin 3.75 mg given every 4 weeks in addition to cyclophosphamide-doxorubicin-based chemotherapy was compared with the chemotherapy regimen alone. Primary study outcomes were protection of ovarian function, number of participants reporting one or more adverse drug reactions, or percentage of participants with a suppressive effect of leuprorelin on serum estradiol to menopausal levels.

### *Protection of ovarian function and resumption of menses*

A single randomized controlled trial comparing chemotherapy alone and chemotherapy plus leuprorelin was conducted in pre-menopausal Chinese women with stage I to III breast cancer (Recchia et al., 2015) (Table 1).

Compared to chemotherapy alone, patients administered leuprorelin were more likely to resume normal menses within 12-months of chemotherapy (GLOBOCAN, 2016). In an open-label study, 62% and 82% of patients experienced resumed menses within six-months and three-years post-chemotherapy, respectively (Recchia et al., 2015). Two patients in the open label study became pregnant within one year post-chemotherapy. One gave birth to a healthy infant, in the other, the pregnancy was terminated (no reason was given) (Recchia et al., 2015).

### *Early menopause*

Leuprorelin was shown to effectively preserve ovarian function after chemotherapy, with 28.7% of women in the chemotherapy alone arm, and 16.9% of women in the leuprorelin-chemotherapy arm experiencing early menopause ( $p < 0.01$ ) (GLOBOCAN, 2016). Women receiving cyclophosphamide-doxorubicin with a taxane were less likely to experience premature menopause (GLOBOCAN, 2016). In an open-label study, no patients exhibited menopausal symptoms following leuprorelin use (GLOBOCAN, 2016).

### *Gonadotrophin levels*

Leuprorelin can reduce E2 levels to menopausal levels. 10, 11 Mean values of E2 are significantly decreased following chemotherapy regardless of leuprorelin use (GLOBOCAN, 2016). Mean values of FSH are significantly increased, however, values in patients receiving chemotherapy alone are higher than those in women receiving concomitant leuprorelin (GLOBOCAN, 2016). In a single arm study from Korea, increases in FSH and LH peak at 3-months post chemotherapy, and return to baseline levels by six months (Recchia et al., 2015). This was regardless of tamoxifen use (Recchia et al., 2015).

### *Survival and tumor response*

Following 96-weeks treatment with leuprorelin, the progression free survival was 50%, and the recurrence free survival was 95% (Lambertini et al., 2015). Similar disease free survival was observed in those treated with 6-monthly or 3-monthly injections (97% and 98%, respectively) (Ruddy et al., 2014). Distant disease free survival were reported. 13 At week 96, 15% of patient treated with leuprorelin achieved a best overall response (Lambertini et al., 2015).

### *Adverse effects*

Typically, the majority of adverse effects are related to concomitant chemotherapy (GLOBOCAN, 2016). Women administered leuprorelin experienced grade 1 or 2 adverse events including hot flush, mood swings and urogenital symptoms (GLOBOCAN, 2016).

In the study comparing 3-monthly and 6-monthly injections, serious adverse events that were considered to be related to leuprorelin included interstitial lung disease ( $n=3$ ) and anal fistula.

Adverse events associated with leuprorelin included injection site reactions, hot flushes, nasopharyngitis, radiation skin injury, decreased white blood cell counts, headache and arthralgia (Lambertini et al., 2015; Park

Table 1. Studies of leuprorelin in Asian populations

Study	Country	Population	Intervention	Comparator	Outcomes	Results
Song et al 7 RCT	China	Premenopausal women aged 18-45 with stage I to III breast cancer and regular menstrual cycle prior to study entry n=183	Chemotherapy + leuprolide acetate 3.75 mg sc every four weeks	Chemotherapy alone	FSH levels; estradiol (E <sub>2</sub> ) levels; and menstrual activity at 3, 6, 9 and 12 months Early menopause defined as FSH > 40 mIU/mL and E <sub>2</sub> < 20 pg/mL in the absence of resumption of menstrual activity within 12 months after the end of chemotherapy. Effective treatment was defined as resumption of menstrual activity (regardless of FSH level or E <sub>2</sub> level) or occurrence of FSH level 40 mIU/ml and E <sub>2</sub> level [ 20 pg/ml in the absence of resumption of menstrual activity during the 12-month follow-up after the end of chemotherapy.	Early menopause occurred in 16.9% in the leuprolide-chemotherapy arm and 28.7 % in the chemotherapy alone arm (p<0.01). Resumption of menses occurred in 60% in the leuprolide-chemotherapy arm and 41% in the chemotherapy alone arm (p<0.01). The median time to resumption of menses was 9.2 months in the leuprolide-chemotherapy arm and not reached in the chemotherapy alone arm. Adverse effects were mostly related to chemotherapy. In the leuprolide group, patients reported hot flush, mood swings, and urogenital symptoms of Grade I or II.
Park et al 12 OL	Korea	Women of reproductive age (< 35 years) with adenocarcinoma of the breast stage I to III N=22	Chemotherapy + leuprorelin 3.75 mg sc	-	Hormone levels at 1, 3 and 6 months after completion of chemotherapy	Mean serum levels of FSH and LH were similar to baseline 6 months after completion of chemotherapy
Takeda 10 NCT02154139 OL	Japan	Premenopausal women with breast cancer N=644	Leuprorelin 11.25 mg sc three monthly for 96 weeks		Adverse events, best response, progression free survival (PFS), recurrence free survival	128 patients reported adverse events, and there were 20 serious adverse events. Best overall response at week 96: 15% PFS at week 96: 50% RFS at week 96: 95%
Kurebayashi et al 11 RCT	Japan	Premenopausal women with estrogen receptor positive or progesterone receptor positive breast cancer N=150	Leuprorelin 22.5 mg 24-weekly sc for up to 96 weeks	Leuprorelin 11.25 mg 12-weekly sc for up to 96 weeks	Hormone levels, disease free survival, distant disease free survival, serum levels, QT interval	Menopausal levels of E <sub>2</sub> were achieved in both a 6-monthly and 3-monthly arms (98% vs 96%). LH and FSH suppressed to ≤ 1 and ≤ 2.5 mIU/mL, respectively from week 4 and remained low through to week 96. DFS at week 96: 97% and 98% (6-monthly and 3-monthly, respectively). DDFS at week 96: 99% and 99% (6-monthly and 3-monthly, respectively).

E<sub>2</sub>, estradiol; OL, open-label; RCT, randomized controlled trial; sc, subcutaneous

et al., 2010). Injection site swelling is more common in patients receiving 6-monthly injections (Park et al., 2010).

Following administration of leuprorelin, QT correction formula (QTcF) intervals declined for the first six hours, and prolonged QTcF intervals of 10 milliseconds were observed from week 4 to 96 following both 3-monthly and 6-monthly injections (Park et al., 2010). Reductions in bone mineral density of approximately 8% were observed over the 96 week treatment period (Park et al., 2010).

## Discussion

Leuprorelin is a synthetic analogue of naturally occurring gonadotropin-releasing hormone, a potent inhibitor of pituitary gonadotropin secretion when given continuously at therapeutic doses. Leuprorelin increases circulating levels of luteinizing hormone and

follicle-stimulating hormone, leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol [E<sub>2</sub>] in premenopausal females). However, continuous administration of leuprorelin results in decreased levels of LH and FSH, and reduces testosterone levels to below the castrate threshold in males (≤ 50 ng/dL), usually within 2 to 4 weeks from initiation of treatment.

To date, only four studies have reported data on leuprorelin use in Asian women with breast cancer. Of these, only three have been published. Two were conducted in Japan, (Lambertini et al., 2015; Park et al., 2010) one in Korea (Recchia et al., 2015) and one in China (GLOBOCAN, 2016). Leuprorelin was administered every 4 weeks (3.75 mg) (GLOBOCAN, 2016; Recchia et al., 2015), every 12-weeks, (Lambertini et al., 2015; Park et al., 2010) or every 24-weeks (Park et al., 2010).

In all of the studies, leuprorelin was administered either with adjuvant chemotherapy or hormonal therapy. Only one study was randomized against a non-leuprorelin arm (GLOBOCAN, 2016).

In women with hormone sensitive cancers, suppression of estrogen may lead to prolonged disease-free survival in premenopausal women (Song et al., 2016; Virani et al., 2014). However, this is at the expense of fertility. Preservation of fertility is important to premenopausal women with malignant tumors (Wong et al., 2015). Traditional approaches to fertility preservation include cryopreservation of oocytes, fertilized embryos and ovarian tissue (Wong et al., 2015). GnRH agonists are recommended for premenopausal patients undergoing chemotherapy who wish to preserve ovarian function. Importantly, women have been able to become pregnant and have successful pregnancy outcomes following surgery, chemotherapy and leuprorelin treatment.

Others have reported success treating patients with luteinizing hormone releasing hormone analogues in women who are premenopausal with breast cancer (Zhang et al., 2017). Treatment with luteinizing hormone releasing hormone analogues also appeared to improve the expected disease-free survival and overall survival (Zhang et al., 2017). Despite this, extended therapy with a GnRH agonist is not without difficulty, as extended therapy may not be acceptable to some women due to the side effects of treatment (such as hot flushes, vaginal dryness and pain (Zhou et al., 2015).

There are several limitations to our review. While the approach to the literature retrieval was systematic, we only included studies that were published in English, which may bias the results, particularly when considering the fact that we are focusing on an Asian population. Secondly, limited statistical analyses were provided for the two unpublished studies (Lambertini et al., 2015; Ruddy et al., 2014), One study has subsequently been published, and is included (Park et al., 2010).

In conclusion, a limited number of studies have investigated leuprorelin for the treatment of patients with breast cancer in Asia. In these studies, leuprorelin was shown to preserve ovarian function, reduce symptoms of ovarian failure, reduce the occurrence of early menopause as well as time to resumption of menses, and reduce E2 concentrations to menopausal levels.

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#### Conflict of interest declaration

HJY and WH have no conflicts of interest to declare.

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