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Leuprorelin acetate for the preservation of ovarian function in premenopausal women with neoplastic disease undergoing chemotherapy

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LAY SUMMARY

Ovarian failure resulting in infertility is a common toxic effect of chemotherapy in cancer patients treated during their reproductive years. Chemotherapy causes premature ovarian failure due to impaired ovarian follicular maturation and/or direct immature follicle loss. The extent of damage depends on the age and pre-treatment ovarian reserve of the patient, and the type and dose of chemotherapy administered. Current options to preserve fertility in young patients who must undergo chemotherapy include cryopreservation strategies ('egg freezing') which can often be complicated and costly.

Leuprorelin acetate is a gonadotropin-releasing hormone (GnRH) analogue that may preserve ovarian function by preventing early stage development of ovarian follicles from maturation. This may decrease the number of follicles that are vulnerable to chemotherapy. The protective effects of GnRH analogues have also been associated with a decrease in utero-ovarian blood flow which leads to decreased exposure of the ovaries to the chemotherapeutic agents. If licensed, leuprorelin acetate, given by injection, may offer a simpler, less invasive and less expensive alternative when compared to current strategies for preserving ovarian function in women undergoing chemotherapy.

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TARGET GROUP

Preservation of ovarian function in premenopausal women with neoplastic disease undergoing chemotherapy treatment

TECHNOLOGY

DESCRIPTION

Leuprorelin acetate (Prostap DCS) is a synthetic nonapeptide that is a potent gonadotropin-releasing hormone (GnRH) receptor agonist. As its basic mechanism of action, leuprolide acetate suppresses gonadotrope secretion of luteinizing hormone and follicle-stimulating hormone that subsequently suppresses gonadal sex steroid production.[1]

In the preservation of ovarian function, it has been suggested that GnRH analogues work by suppressing gonadotropin levels to stimulate pre-pubertal hormonal milieu and subsequently preventing primordial follicles from maturation and therefore decreasing the number of follicles that are more vulnerable to chemotherapy. The protective effect of GnRH analogues have also been associated with decrease in utero-ovarian perfusion which leads to decreased exposure of the ovaries to the chemotherapeutic agents, upregulation of intragonadal anti-apoptotic molecules such as sphingosine-1-phosphate, and protection of the undifferentiated germline stem cells.[2] GnRH analogues may also protect ovarian function by directly activating GnRH receptors on ovaries, although the extent of the mechanism of action remains largely theoretical and requires further clinical study.[3,4]

In a phase III trial (POEMS, NCT00068601) the GnRH analogue goserelin acetate (Zoladex) was administered in combination with chemotherapy and was associated with less premature ovarian failure (POF) and more pregnancies, with improved disease-free survival and overall survival in premenopausal women with breast cancer.[5,6] Furthermore, the results of a phase III trial (PROMISE-GIM6, NCT00311636) found that the use of GnRH analogue triptorelin acetate (Decapeptyl) during chemotherapy in premenopausal patients with early-stage breast cancer reduced the occurrence of chemotherapy-induced early menopause.[7,8]

A phase II study of leuprorelin acetate on ovarian function preservation in premenopausal patients with breast cancer provided clinical evidence that treatment before and during adjuvant chemotherapy reduced the risk of developing premature ovarian failure in premenopausal patients with breast cancer.[4] Further clinical trials are warranted to assess the appropriate patient group that will benefit most from ovarian suppression treatment.[2] The company propose a treatment dose of leuprorelin acetate 3.75mg every calendar month or 11.25mg every three calendar months for duration of chemotherapy therapy to potentially preserve ovarian function in premenopausal women with neoplastic disease.[a]

Leuprorelin acetate (Prostap SR DCS, Prostap 3 DCS) is currently licensed in the UK for the following indications:[9,10]

- Metastatic prostate cancer
- Locally advanced prostate cancer, as an alternative to surgical castration

[a] Information provided by company on UK PharmaScan

- As an adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer
- As an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression
- As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer
- Management of endometriosis, including pain relief and reduction of endometriotic lesions
- In children – treatment of central precocious puberty (girls under 9 years of age, boys under 10 years of age)

Leuprorelin acetate (Prostap SR DCS) is currently licensed in the UK for the following additional indications:

- Endometrial preparation prior to intrauterine surgical procedures including endometrial ablation or resection.
- Preoperative management of uterine fibroids to reduce their size and associated bleeding

In women, adverse effects occurring most frequently (≥1/10 to ≥1/100 to <1/10) with leuprorelin acetate are associated with hypo-estrogenism; the most frequently reported are hot flushes, mood swings including depression (occasionally severe), and vaginal dryness.[9,10]

INNOVATION and/or ADVANTAGES

No standard method for preventing chemotherapy-induced premature ovarian failure (POF) has been established.[11] Several approaches have been attempted to preserve fertility in young patients who must undergo chemotherapy, including cryopreservation strategies which can often be complicated and costly. GnHR analogue treatment has been proposed to be a less invasive and easier way to prevent the cytotoxic effects of chemotherapeutics on ovaries.[4]

GnRH analogue induced ovarian suppression offers advantages in that it does not require a male partner, is simple to administer, does not require delaying chemotherapy, and is less invasive and less expensive.[7] If licensed, leuprorelin acetate will offer an additional treatment option for the preservation of ovarian function in premenopausal women with neoplastic disease undergoing chemotherapy treatment who currently have limited effective therapies available.

DEVELOPER

Takeda UK Ltd

PATIENT GROUP

BACKGROUND

Early ovarian failure is an important and potentially devastating long-term toxic effect of chemotherapy. Apart from the essential role of ovarian function in preserving fertility, premature ovarian failure is associated with vasomotor symptoms, osteoporosis, urogenital symptoms and heart disease. Concerns about fertility may also influence treatment choices for young women with neoplastic disease, in addition to the negative psychosocial effects related to such reproductive changes. [12,17] Incidences of premature menopause are dependent on the type of chemotherapy and

the patient's age. Chemotherapy regimens are associated with an incidence of long-term amenorrhea of at least 40%, with a more pronounced effect being associated with the use of regimens containing a high cumulative dose of cyclophosphamide.[7]

While breast cancer indications are the current focus of GnRH analogue research, additional studies have also evaluated their application for preservation of ovarian function in childhood cancer patients, ovarian cancer, systemic lupus erythematosus, and after hematopoietic cell transplantation (among others).[13,14,15,16] Although there is no clear definition of chemotherapy-induced ovarian failure, irreversible amenorrhoea lasting for several months (>12 months) following chemotherapy and a follicle stimulating hormone level of ≥30 MIU/mL in the presence of a negative pregnancy test is considered an appropriate characterisation.[17]

CLINICAL NEED and BURDEN OF DISEASE

Chemotherapy with alkylating agents, such as cyclophosphamide, is associated with the greatest risk of amenorrhoea.[18] Paclitaxel (Taxol), also used in the treatment of breast cancer, affects ovarian function to a lesser degree. Chemotherapy with cyclophosphamide, methotrexate and 5 fluorouracil has been shown to result in the loss of ovarian function in 33% of women under age 30, 50% of women aged 30-35, 75% of women aged 35-40, and 95% of women over age 40.[19]

The population likely to be eligible to receive leuprorelin acetate could not be estimated from available published sources. The company estimate that patients would require injections every month or every three months for the duration of chemotherapy treatment. However, as protection of fertility is not confirmed by preserving ovarian function in this way, the number of patients eligible for treatment are likely to be small.[b]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/A.
- NHS England. 2013/14 NHS Standard Contract for cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- Fertility Preservation in Patients with Cancer: ASCO Clinical Practice Guideline (Updated), 2018[20]
- The ESHRE Guideline Group on POI. ESHRE Guideline: Management of women with premature ovarian insufficiency, 2015[21]
- The Journal of Clinical Endocrinology & Metabolism. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline, 2015[22]

[b] Information provided by company on UK PharmaScan.

CURRENT TREATMENT OPTIONS

Besides the fertility preservation methods that utilize assisted reproductive technologies such as embryo, oocyte, and ovarian tissue cryopreservation, another suggested strategy for fertility preservation is suppression of ovarian ovulatory function by GnHR agonist administration before and during chemotherapy.[12] Goserelin acetate (Zoladex) and triptorelin acetate (Decapeptyl) are GnRH agonists currently licensed in the UK for a range of cancer indications with a similar mechanism of action to leuprorelin acetate.[23,24] In instances of operable breast cancer, both goserelin acetate and triptorelin acetate co-treatment with different regimens of chemotherapy have been trialled with inconsistent efficacy in the preservation of ovarian function.[12]

However, a systematic review and meta-analysis to determine efficacy of GnRH agonists administered concurrently with chemotherapy for ovarian function preservation in premenopausal women undergoing chemotherapy for early stage breast cancer found that the use of GnRH agonists was associated with a higher rate of recovery of regular menses after 6 months and at least 12 months following the last chemotherapy cycle. The use of GnRH agonists was also associated with a higher number of pregnancies, although this outcome was not uniformly reported.[25]

Recently published clinical practice guidelines for fertility preservation in patients with cancer found there to be conflicting evidence to support the recommendation of GnRH agonists and other means of ovarian suppression for fertility preservation. When proven fertility preservation methods are not feasible, and in the setting of young women with breast cancer, GnRH agonists may be offered to patients in the hope of reducing the likelihood of chemotherapy induced ovarian insufficiency. As there is insufficient evidence regarding effectiveness, and further data establishing safety and long term efficacy are needed, it is recommended GnRH agonists should not yet be used in place of proven fertility preservation methods.[20]

EFFICACY and SAFETY

There are currently no new clinical trials investigating leuprorelin acetate for the preservation of ovarian function in premenopausal women with neoplastic disease undergoing chemotherapy treatment.

Trial	POEMS, NCT00068601; cyclophosphamide + goserelin acetate; phase III
Sponsor	Southwest Oncology Group
Status	Published
Source of Information	Publication[5], Trial Registry[6]
Location	3 EU countries (not including UK), Switzerland, Australia and New Zealand
Design	Randomised, active-controlled
Participants	n=257; aged 18-49 years; female; premenopausal; breast cancer stage I-IIIA ER/PR-negative; to be treated with chemotherapy (CT)
Schedule	Randomized (1:1) to receive standard cyclophosphamide-containing CT with or without monthly goserelin acetate administered at a dose of 3.6 mg subcutaneously every 4 weeks beginning 1 week before the initial CT dose and continued to within 2 weeks before or after the final CT dose
Follow-up	Not stated

Primary Outcomes	• Rate of POF at 2 Years [Time frame: 2 years] Ovarian failure at two years is defined as amenorrhea (absence of menstrual bleeding) for the preceding six months AND the presence of follicle-stimulating hormone (FSH) in the post-menopausal range
Secondary Outcomes	• Rate of Ovarian Dysfunction at 2 Years [Time frame: 2 years] Ovarian dysfunction is defined as amenorrhea for the preceding three months and the presence of FSH, estradiol and/or inhibin B levels in the postmenopausal range. • Rate of Ovarian Dysfunction at 1 Year [Time frame: 1 year] Ovarian dysfunction is defined as amenorrhea for the preceding three months and the presence of FSH, estradiol and/or inhibin B levels in the postmenopausal range. • Other – Ovarian Reserve at 1 and 2 years [Time frame: 1 and 2 years] Measurement of ovarian reserve will consist of "Day 2-4" levels of FSH, estradiol and inhibin B during Month 12/13 and Month 24/25 (or if amenorrheic, anytime during Month 12/13 and Month 24/25)
Key Results	Luteinizing hormone releasing hormone (LHRH) analog administration with CT was associated with less POF and more pregnancies, with improved disease-free survival and overall survival.
Adverse effects (AEs)	Of the 103 patients who could be evaluated for adverse events in the goserelin group, 1 had a grade 4 toxic effect (thromboembolism) and 6 had grade 3 toxic effects.
Expected reporting date	-

Trial	PROMISE-GIM6, NCT00311636; triptorelin + chemotherapy; phase III
Sponsor	Gruppo Italiano Mammella (GIM)
Status	Published
Source of Information	Publication[7], Trial Registry[8]
Location	Italy
Design	Randomised, parallel assignment
Participants	n=281; aged 18-45 years; female; premenopausal; breast cancer stage I-III; to be treated with (neo)adjuvant CT
Schedule	Randomized (1:1) to receive CT with or without triptorelin administered intramuscularly at a dose of 3.75 mg at least 1 week before the start of chemotherapy and then every 4 weeks for the duration of chemotherapy.
Follow-up	12 months
Primary Outcomes	• Chemotherapy-induced early menopause as measured by follicle-stimulating hormone, 17 beta estradiol levels, and menstrual activity resumption at 1 year following the completion of chemotherapy
Secondary Outcomes	• Toxicity as measured by Common Toxicity Criteria at each chemotherapy course
Key Results	The clinical and tumor characteristics of the 133 patients randomized to chemotherapy alone and the 148 patients randomized to chemotherapy plus triptorelin were similar. Twelve months after the last cycle of chemotherapy (last follow-up, August 18, 2009), the rate of early menopause was 25.9% in the chemotherapy-alone group and 8.9% in the chemotherapy plus triptorelin group, an absolute difference of -17% (95% confidence interval, -26% to -7.9%;

	P < .001). The odds ratio for treatment-related early menopause was 0.28 (95% confidence interval, 0.14 to 0.59; P < .001).
Adverse effects (AEs)	Not stated
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

Leuprorelin acetate (Prostap SR DCS) is already marketed in the UK; 1 x 3.75mg powder and solvent for suspension for injection pre-filled syringe has a NHS indicative price of £75.24. Leuprorelin acetate (Prostap 3 DCS) is additionally marketed in the UK; 1 x 11.25mg powder and solvent for suspension for injection pre-filled syringe has a NHS indicative price of £225.72.[26]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other: *uncertain unit cost*

☐ None identified

OTHER ISSUES

☒ Clinical uncertainty or other research question identified: *insufficient evidence regarding effectiveness, further data establishing safety and long-term efficacy needed*

☐ None identified

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