Short Communication

A pilot study to assess the use of the gonadotrophin antagonist cetrorelix in preserving ovarian function during chemotherapy

Julie WHITEHEAD,[1,2] Manuela G. TOLEDO[1,2] and Catharyn J. STERN[1,2]

[1]*Melbourne IVF, Melbourne, and* [2]*Reproductive Services, The Royal Women's Hospital, Parkville, Vic., Australia*

Cyclophosphamide treatment can cause premature ovarian failure. This pilot study evaluates the protective effect of the gonadotrophin releasing hormone (GnRH) antagonist, cetrorelix, on ovarian function, when used during cyclophosphamide chemotherapy in women aged 18–35. Primary outcomes measured were serum follicle stimulating hormone (FSH) and inhibin prior to and at 6 and 12 months after chemotherapy. Secondary outcomes were hormonal evidence of a suppressive effect and the side effect profile.

Key words: chemotherapy, gonadotrophin releasing hormone (GnRH), ovarian function.

Introduction

Chemotherapeutic agents such as cyclophosphamide can cause impaired ovarian function and premature ovarian failure.[1] Studies in animal models and women demonstrate that gonadotrophin-releasing hormone (GnRH) agonists such as goserelin administered during chemotherapy may have a protective effect on ovarian function although the exact mechanism of action is still being debated.[2–5]

Gonadotrophin releasing hormone is synthesised in the hypothalamus and released in a pulsatile fashion. It binds to GnRH receptors on the anterior pituitary gland to promote the release of follicle stimulating hormone (FSH) and luteinising hormone (LH). The receptors are sensitive to the levels of GnRH in a time- and dose-dependent manner.[6,7] Prolonged exposure of the anterior pituitary to high concentrations of GnRH decreases the response of those cells to any subsequent stimulation by GnRH, leading to the suppression of FSH and LH secretions.[7] Upon administration of a GnRH agonist, there is an initial intense release of stored LH and FSH, which is followed by the downregulation of GnRH receptors and a decrease in LH and FSH levels to the pre-pubertal range. GnRH agonists have a binding affinity for the receptor that is approximately 100–200 times that of endogenous GnRH.[6] The exact mechanism of action of GnRH agonists in protecting the ovary from chemotherapy is not yet known; they are thought to work by a combination of central suppression of gonadotropins at the level of the pituitary, suppression of gonadotropin receptors in the ovary and a local action at the level of the ovary.[3–5,8]

The aim of this pilot study was to evaluate the protective effect of the GnRH antagonist cetrorelix (Cetrotide, Serono, Geneva, Switzerland) when used during potentially toxic doses of chemotherapy in reproductive aged women.

Materials and Methods

Institutional review board approval was obtained. This pilot study consisted of 18 women, aged between 18 and 35, who were diagnosed with either cancer or an autoimmune disease. The conditions included breast cancer, lymphoma, sarcoma and autoimmune diseases requiring potentially toxic doses of cyclophosphamide treatment. Exclusion criteria were pre-bone marrow transplant conditioning chemo-radiotherapy and women assessed to have a poor long-term prognosis.

Women were recruited from the Fertility Preservation Clinic (FPC) at the Royal Women's Hospital and Melbourne IVF. Women were referred to the FPC from oncologists. The clinical work-up included menstrual history, baseline hormonal profile for day 2 FSH (IU/L), oestradiol (pmol/L), inhibin A and B (ng/L) levels and day 21 progesterone (nmol/L) confirming ovulation.

The 18 women were given three doses of 250 μg GnRH antagonist, cetrorelix, every 4 days over 12 days commencing 1–4 days prior to the onset of each chemotherapy cycle (where possible) and for the duration of their chemotherapy. Their hormone profile was measured at each injection time point for the first two cycles and then at 6 and 12 months.

The aims of this pilot study were to observe whether patients receiving a GnRH antagonist concurrently during chemotherapy with cyclophosphamide had preservation of

Correspondence: Dr Julie Whitehead, Fertility Specialist, 108/320 Victoria Parade, East Melbourne, Vic., 3002, Australia. Email: julie.whitehead@mivf.com.au

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ovarian function, as well as the speed of onset of ovarian suppression, and whether there was a tolerable side effect profile.

Primary outcomes measured were resumption of regular menstrual cycles, day 2 serum FSH and inhibin A and B levels at 6 and 12 months after chemotherapy. Secondary outcomes measured were hormonal evidence of suppressive effects of the GnRH antagonist and the side effects of its use.

Results

Our 1-year results for primary outcomes showed that 14/15 (94%) women resumed spontaneous ovulation and menses within 12 months (Table 1). The total cumulative cyclophosphamide dose for these women was 3.4–6.6 g. In addition to cyclophosphamide, all women had at least one other chemotherapy drug during their treatment. Three women failed to complete this pilot study prior to its conclusion. One woman died of metastatic disease prior to the conclusion of the trial. Another withdrew after developing lymphoedema and extensive burns secondary to radiotherapy, while the third woman withdrew after the first treatment cycle with the antagonist owing to severe skin toxicity associated with her chemotherapy regimen. FSH level was evaluated in 14/18 women prior to commencing the trial and was within the normal range (<10 IU/L) with a mean of 5.18 IU/L. In four women, pre-trial FSH was not measured owing to the need to start treatment immediately. A normal day 2 FSH (< 10 IU/L) was recorded in 14/15 (94%) women at 12 months post-trial (mean FSH 6.28; range, 3.8–15 IU/L). Consistent with this, 14/15 (94%) women had progesterone levels in the ovulatory range (mean 55 nmol/L) at 12 months (Table 2). At 12 months, 13/15 (87%) women had normal inhibin A and B levels (Table 1). Assessment of secondary outcomes showed that the main side effect reported was hot flushes. Eleven of 15 (73%) women reported hot flushes only while on the GnRH antagonist, 3/15 (20%) reported no side effects and 1/15 (7%) exhibited persistent hot flushes. The one woman who experienced persistent hot flushes developed evidence of acute ovarian failure (as follow-up was only for up to 18 months we are unable to establish if this is permanent ovarian failure). The hormonal assessments supported these findings. Thirteen of fifteen women did not have regular cycles during treatment, which is consistent with suppression of FSH and LH by the antagonist.

Table 1 Ovarian function at 6 months and 12 months post-treatment

Time point	Normal menstruation (%)	Normal day 2 follicle stimulating hormone (%)	Normal inhibin A (%)	Normal inhibin B (%)
6/12	9/15 (60)	7/15 (47)	7/15 (47)	7/15 (47)
12/12	14/15 (94)	14/15 (94)	13/15 (87)	13/15 (87)

Table 2 Correlation of menstruation with progesterone levels

	Pre-treatment	During treatment	Post-treatment 12/12
Menstruation	15/15 (100%)	9/15 (60%)	14/15 (94%)
Progesterone (nmol/L)	43	8.9	55

NB: Luteal > 15 nmol/L.

Discussion

We were interested in initiating this pilot study as there is some evidence of possible benefit of GnRH agonist use for ovarian protection during chemotherapy in previously reported studies, and there are potential advantages in using an antagonist rather than an agonist.

Cyclophosphamide is used in combination chemotherapy regimens for lymphomas, leukaemias, breast cancer and non-malignant conditions such as systemic lupus erythematosus. Cyclophosphamide specifically targets rapidly dividing cells such as oocytes and granulosa cells.[9]

Gonadotrophin-releasing hormone agonists have a number of side effects because they create a pseudomenopausal state. The immediate side effects are menopausal symptoms such as hot flushes, cessation of menstruation, dry skin and decreased libido.[6,10] A review of studies of bone loss with GnRH agonists concluded that, overall, when used for <6 months, they cause no significant loss of cortical bone and a decrease in trabecular bone density of 2–8%. In many studies, this loss was found to have partly or completely reversed within 6 months of discontinuing treatment.[11]

There have now been several small studies looking at the effectiveness of depot GnRH agonist treatment in preserving ovarian function in women undergoing chemotherapy. In a study by Blumenfeld *et al.*,[12] 28 women with lymphoma were given a depot GnRH agonist concurrently with their chemotherapy; 3.6% developed ovarian failure during a follow-up time of 8 years. A matched historical control group showed a premature ovarian failure rate of 65% ($P < 0.05$). Another study by Blumenfeld *et al.* involved 16 women aged 15–40 with lymphoma given a GnRH agonist with their chemotherapy. Fifteen of sixteen (94%) continued to ovulate during a 4-year follow-up period. The matched historical control group was aged 17–40 years and reported an ovarian failure rate of 61% ($P < 0.01$). During treatment with the GnRH agonist, each woman had LH, oestradiol and progesterone levels measured monthly, and these fell to almost pre-pubertal levels during treatment, demonstrating gonadal suppression. Three of the women in the study group had a transient increase in FSH and LH after the completion of treatment, which is consistent with a subclinical degree of gonadal damage.[13]

The results of our pilot study are similar to those of the study by Blumenfeld *et al.*[13] and potentially support the use of GnRH antagonist use during chemotherapy, where they may exert a protective effect on ovarian function with an acceptable side effect profile.

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