

# Can ovarian function be protected in young women receiving chemotherapy?

**Original article** Recchia F *et al.* (2006) Gonadotropin-releasing hormone analogues added to adjuvant chemotherapy protect ovarian function and improve clinical outcomes in young women with early breast carcinoma. *Cancer* 106: 514–523

## SYNOPSIS

**KEYWORDS** breast cancer, fertility, gonadotropin, ovarian preservation, ovarian protection

### BACKGROUND

Breast cancer in premenopausal women is more often treated with chemotherapy rather than hormone therapy. Ovarian failure leading to early menopause is one of the most important potential adverse effects of adjuvant chemotherapy.

### OBJECTIVES

To evaluate the use of a gonadotropin-releasing hormone (GnRH) analog as ovary protection during adjuvant chemotherapy for high-risk, early breast carcinoma in premenopausal women.

### DESIGN

In this retrospective study, patients with unilateral breast adenocarcinoma who had undergone modified radical mastectomy or breast-conserving surgery plus axillary lymph node dissection between September 1993 and August 2002 were included. Patients had Eastern Cooperative Oncology Group performance status of 0–1, were actively menstruating and were between 18 and 50 years of age.

### INTERVENTION

Patients received goserelin (3.6 mg subcutaneously) 3 weeks following surgery and 1 week before chemotherapy was started, and then every 28 days for 1 year in the first part of the study. In the second part of the study, the same analog was administered at 11.25 mg every 84 days for 2 years. Adjuvant chemotherapy, including methotrexate, cyclophosphamide, 5-fluorouracil, and anthracycline-based regimens, was tailored according to the patient biologic characteristics, and 80 patients

received radiotherapy. Patients with positive estrogen receptor (ER) status following chemotherapy received an aromatase inhibitor during therapy with the GnRH analog.

### OUTCOME MEASURES

The primary outcome measure was the efficacy of GnRH analogs in protecting ovarian function in premenopausal women with early breast carcinoma treated with adjuvant chemotherapy. Secondary outcome measures were disease-free survival (DFS) and overall survival.

### RESULTS

Patients ( $n = 100$ , age range 27–50 years, median age 43 years) were followed for a median of 75 months, by which time all patients had completed chemotherapy and GnRH analog treatment. After treatment was discontinued, 67% (including all the patients younger than 40 years) resumed normal menses with appropriate hormone levels. There were three pregnancies, of which two resulted in the birth of healthy children at term (the other pregnancy was terminated). At the time of analysis 77% of patients were disease-free and 92% were alive. Projected DFS rates at 1, 5 and 10 years were 100%, 84% and 77%, whereas projected overall survival rates were 100%, 96% and 92% respectively. Among the 52% who had ER-positive tumors, 10-year survival rate was 91%, similar to that in the ER-negative group (93%). Patients with ER-negative tumors had a DFS rate of 61%, whereas those with ER-positive tumors had a DFS rate of 89% ( $P = 0.056$ ). None of the 38 patients who received GnRH analog for 2 years developed disease recurrence.

### CONCLUSION

Addition of a GnRH analog to adjuvant chemotherapy benefits premenopausal women with early ER-positive breast carcinoma directly via hormone deprivation, as well as improving the likelihood that normal menses will be resumed in these patients.

## COMMENTARY

Margareta D Pisarska\*  
and Lee-Chuan Kao

Among women diagnosed with breast cancer, 25% are premenopausal.<sup>1</sup> Most will be treated with adjuvant chemotherapy. Although adjuvant treatment results in a 5-year DFS of 81–84% in women with localized breast cancer,<sup>2</sup> long-term adverse effects, such as loss of ovarian function with resultant permanent amenorrhea and infertility, can occur. The average rate of amenorrhea in women of reproductive age is 40% with cyclophosphamide, methotrexate and 5-fluorouracil protocols and 33% with anthracyclines.<sup>3</sup>

Cytotoxic effects of chemotherapy can lead to an initial wave of follicle loss, leading to increases in follicle-stimulating hormone, followed by follicle recruitment and further loss until complete depletion occurs. Continuous exposure to GnRH leads to receptor downregulation and subsequent suppression of gonadotropin release from the pituitary gland, resulting in complete suppression of ovarian function. This can confer protection against the gonadotoxic effects of chemotherapy, as demonstrated in animal models.<sup>4</sup> Protection may occur directly through ovarian GnRH receptors or follicle-stimulating hormone or luteinizing hormone receptors present in the presumed gonadotropin-independent primordial and primary follicles.<sup>4</sup>

Recchia *et al.* reported on 100 premenopausal women with breast cancer who received a GnRH analog for ovarian protection during chemotherapy. Ten-year survival rate was 91% in the ER-positive tumor group, similar to the 10-year survival rate of 93% in the ER-negative group. A number of randomized controlled trials, such as the Zoladex® Early Breast Cancer Research Association study<sup>5</sup> and the International Breast Cancer Study Group Trial VIII,<sup>2</sup> have demonstrated that GnRH analogs as adjuvant treatment for women with ER-positive breast cancer are equivalent to chemotherapeutic regimens in terms of DFS and overall survival. A smaller randomized trial comparing adjuvant chemotherapy and ovarian function suppression with endocrine therapy alone showed no difference in 4-year DFS between the two groups.<sup>6</sup> As demonstrated by Recchia *et al.*, similar 10-year survival was present in patients with ER-negative disease compared with those with ER-positive disease. Recchia *et al.* found that

all women of reproductive age resumed menses and hormonal levels normalized after therapy and remained normal for up to 75 months mean follow up. Thus, acute ovarian failure as well as premature menopause<sup>7</sup> was prevented. This prevention of premature menopause does not necessarily translate to fertility preservation, however. Normally, fertility declines rapidly 15 years before the onset of amenorrhea associated with menopause, because of a diminished ovarian reserve. It is difficult to determine if the administration of a GnRH analog, which may preserve ovarian function, will also preserve fertility, since Recchia *et al.* reported on only three pregnancies. With increasing DFS, options of fertility preservation should be planned with the surgeon, oncologist and reproductive endocrinologist prior to chemotherapy. Until more information becomes available from the ongoing randomized controlled trials on the use of GnRH analogs (Breast International Group/North American Breast Cancer Intergroup SOFT, TEXT and PERCHE studies<sup>2</sup>), results available from the present study provide some important information regarding resumption of ovarian function in women treated with adjuvant chemotherapy.

## References

- 1 Jemal A *et al.* (2004) American Cancer Society. Cancer statistics, 2004. *CA Cancer J Clin* **54**: 8–29
- 2 Castiglione-Gertsch M *et al.* (2003) Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. *J Natl Cancer Inst* **95**: 1833–1846
- 3 Stern CJ *et al.* (2006) Fertility preservation in female oncology patients. *Aust N Z J Obstet Gynaecol* **46**: 15–23
- 4 Blumenfeld Z and Eckman A (2005) Preservation of fertility and ovarian function and minimization of chemotherapy-induced gonadotoxicity in young women by GnRH-a. *J Natl Cancer Inst Monogr* **34**: 40–43
- 5 Kaufmann M *et al.* (2003) Survival analyses from the ZEBRA study. Goserelin (Zoladex®) versus CMF in premenopausal women with node-positive breast cancer. *Eur J Cancer* **39**: 1711–1717
- 6 International Breast Cancer Study Group (2001) Randomized controlled trial of ovarian function suppression plus tamoxifen versus the same endocrine therapy plus chemotherapy: is chemotherapy necessary for premenopausal women with node-positive, endocrine responsive breast cancer? First results of International Breast Cancer Study Group Trial 11–93. *The Breast* **10** (Suppl 3): 130–138
- 7 Sklar C (2005) Maintenance of ovarian function and risk of premature menopause related to cancer treatment. *J Natl Cancer Inst Monogr* **34**: 25–27

MD Pisarska and L-C Kao are Co-Directors for The Center for Fertility and Reproductive Medicine at Cedars-Sinai Medical Center, and Assistant Professors at The David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.

## Acknowledgments

The synopsis was written by Petra Roberts, Associate Editor, Nature Clinical Practice.

## Competing interests

The authors declared they have no competing interests.

## Correspondence

\*Department of Obstetrics and Gynecology Cedars-Sinai Medical Center/David Geffen School of Medicine at UCLA Suite 160W 8635 West Third Street Los Angeles CA 90048 USA pisarskam@cshs.org

Received 22 May 2006

Accepted 25 July 2006

www.nature.com/clinicalpractice  
doi:10.1038/nconpc0592

## PRACTICE POINT

Gonadotropin-releasing hormone analogs seem well tolerated in women undergoing adjuvant chemotherapy for early breast cancer and may confer ovarian protection from chemotherapy