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therapy, which might reduce the extent of disease before surgery"; might neoadjuvant be a way to "short cut" the disease? In a time where there is much debate as to which is the better route to R0, primary debulking or neoadjuvant treatment, this study questions the putative end points of these approaches: the reliable clinical significance of attaining R0 after surgery.—LVL)

Goserelin for Ovarian Protection During Breast-Cancer Adjuvant Chemotherapy

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ABSTRACT

Premature ovarian failure is a devastating long-term toxic effect of chemotherapy for premenopausal women. The survival benefit of adjuvant chemotherapy in young women with operable hormone receptor–negative breast cancer is well known, but concern over becoming infertile may influence the choice of treatment for many women. A number of trials have investigated the combined use of a gonadotropin-releasing hormone (GnRH) agonist and adjuvant chemotherapy in an attempt to protect ovarian function in premenopausal women. Results of such studies were mixed, and there were few data on pregnancy outcomes.

The aim of this randomized trial was to determine whether administration of the GnRH agonist goserelin with chemotherapy would reduce the rate of ovarian failure after adjuvant or neoadjuvant treatment of hormone-receptor–negative early-stage breast cancer. A total of 257 premenopausal women with operable hormone receptor–negative breast cancer were randomized to receive standard chemotherapy with goserelin (goserelin group) or standard chemotherapy without goserelin (chemotherapy-alone group). The rate of ovarian failure at 2 years was the primary study end point. Ovarian failure was defined as the absence of menses for the preceding 6 months and follicle-stimulating hormone levels in the postmenopausal range at 2 years. Conditional logistic regression was used to compare rates. Secondary end points evaluated included pregnancy outcomes and disease-free and overall survival.

Of the 257 patients, 218 were eligible and could be evaluated: 113 in the chemotherapy-alone group and 105 in the goserelin group. Complete primary end-point data were available for 135 of the 218 patients who could be evaluated. Among these, the ovarian failure rate was 8% in the goserelin group and 22% in the chemotherapy-alone group; the odds ratio was 0.30, with a 95% confidence interval of 0.09 to 0.97; 2-sided $P = 0.04$. To determine the effect of the missing primary end-point data on the main study findings, sensitivity analyses were performed. The results of these analyses showed that the missing data had no significant effect on the association between treatment and stratification variables (age and planned chemotherapy regimen). Among the 218 patients who could be evaluated, more women became pregnant in the goserelin group than in the chemotherapy-alone group (21% vs 11%, $P = 0.03$). Kaplan-Meier curves showed that more women in the goserelin group had improved disease-free survival ($P = 0.04$) and overall survival ($P = 0.05$).

Consistent with the findings of previous randomized trials, these data suggest that administration of a GnRH agonist with chemotherapy protects ovarian function, reducing the risk of early menopause and improving prospects for fertility. Although missing primary-end-point data weaken interpretation of the findings, there is no evidence that the missing data influenced the relative comparison between randomized groups.

EDITORIAL COMMENT

(In 2014, 1.6 million new cancers were diagnosed in the United States. Of the women diagnosed with cancer, 10% were younger than 40 years. Surgery and chemotherapy put the ovary at jeopardy for early failure. In addition, for this population, maintenance of fertility may still be important. The seriousness of this issue came to the forefront in 2006 with recognition of the specialty of oncofertility and creation of an oncofertility consortium by the National Institutes of Health. In addition, in 2006, the American Society of Clinical Oncology acknowledged this area of concern and published guidelines addressing the need for counseling of young patients about to start cancer treatment.

In the current study Dr Moore and colleagues report results of their prospective randomized controlled trial of treatment with goserelin acetate for ovarian protection in breast cancer patients undergoing adjuvant chemotherapy. Numerous retrospective and small studies have supported the use of GNRH agonists for ovarian protection during chemotherapy. This is the largest prospective trial to date. Patients were older (median age, 37 years), and most received 6 to 8 cycles of anthracycline-based chemotherapy. In this study, the outcome is measured as ovarian failure and pregnancy outcome as well as disease-free and overall survival. They found the ovarian failure rate was two thirds less in the goserelin-treated group, and the pregnancy rate, although low, was also double in this group as well. They conclude that treatment with goserelin acetate during chemotherapy protects against ovarian failure, thereby "reducing the risk of early menopause and improving prospects for fertility."

Assisted reproductive technology has come a long way from Dolly the sheep. In particular, advancement to improve the lot of ovarian cancers patients at risk of losing fertility has advanced tremendously. For patients who have a partner, embryos can be frozen successfully within 2 to 3 weeks of stepping into clinic. Similarly, eggs without fertilization (no sperm contribution) can be stored in the same amount of time. The benefit of this approach is the embryos/eggs preserve the functional age from the time of transfer. Alternatively, ovarian protection with use of GNRH agonist goserelin or leuprolide acetate permits ovarian function to continue. Eggs/embryo will be more aged, as patients will need to complete chemotherapy before embarking on conception.

While this study focused on breast cancer patients who were older and received anthracycline-based chemotherapy, these results are probably applicable to patients with gynecologic cancers at risk of losing ovarian function. Luckily, regimens used to treat gynecologic cancers such as bleomycin/etoposide/platin or paclitaxel/carboplatin are associated with decreased fertility risk when compared with breast cancer regimens containing alkylating agents. Additional assisted reproductive technologies undergoing development that would be applicable to this group of patients include future freezing of follicles without antral stimulation and mitochondrial/nuclear transfer of DNA content. In addition it is important to note that surgery for young gynecologic oncology patients has also been adapted in recognition of the need to preserve fertility. Fertility-sparing ovarian cancer staging, possible preservation of ovaries in early endometrial cancers, and preservation of contralateral ovaries in select germ cell cases are examples of surgical refinement acknowledging and respecting the need for young women to maintain their fertility.

In 2015, there are several maneuvers to maintain fertility options in women who develop cancer. The goal is to make the extra effort to inform them of these options and integrate consultation with an oncofertility specialist into their treatment plan.—LVL)