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CORRESPONDENCE

Role of Gonadotropin-Releasing Hormone Analog in the Management of Male Metastatic Breast Cancer Is Uncertain

Drs Giordano and Hortobagyi presented two interesting patients with metastatic male breast cancer who responded to a combination of the gonadotropin-releasing hormone (GnRH) analog leuprolide acetate plus an aromatase inhibitor.[1] They pointed out that suppression of estrogen production in male patients by monotherapy using aromastase inhibitors may be suboptimal because the resultant central estrogen deprivation leads to increased production of follicle stimulating hormone. This drives testicular testosterone production, which in turn becomes a substrate for peripheral estrogen production through aromatisation, forming a deleterious feedback loop. They thus hypothesized that the addition of a GnRH analog could abrogate this feedback mechanism.

We report herein a male patient with metastatic breast cancer who received the combination of goserelin and letrozole with minor disease response.

The patient was a 59-year-old man initially diagnosed with right-sided T1bN0M0 estrogen receptor– and progesterone receptor–positive, HER-2/*neu*–negative breast cancer. He was treated with modified radical mastectomy followed by adjuvant tamoxifen. Three and a half years later, he developed progressive exertional breathlessness and was found to have cytology proven moderate left malignant pleural effusion, bilateral small volume lung metastases, and lytic metastases in the thoracic spine. CA-153 was elevated at 47 u/mL (range, $<$ 26 u/mL).

He received goserelin and letrozole in addition to monthly pamidronate for 6 months. While he improved clinically with reduced volume of chest tube drainage and increased effort tolerance, there was gradual increase in CA-153 from 47 to 53 u/mL and carcinoembryonic antigen from 2.4 to 3.8 ng/mL in addition to computed tomography–documented progression in a representative left lingular lobe lung mass from 2.4 to 3.6 cm over a 24-week period.

At this point, letrozole was discontinued, and he received exemestane and goserelin for the next 6 months. During this period, there was again progressive increase in CA-153 from 53 to 101 u/mL and carcinoembryonic antigen from 4.1 to 5.4 ng/mL. Serial computed tomography scans showed new lung nodules in the right lower lobe and left upper lobe.

Third-line endocrine therapy with fulvestrant and goserelin was planned in view of low volume visceral metastases, slow pace of disease, and relative paucity of symptoms.

It is noteworthy that in men, approximately 80% of circulating estrogens are derived from peripheral aromatization of testicular and adrenal androgens, with direct production from the testes accounting for the remaining 20%.[2] The impact of GnRH analogs on direct testicular production of estrogens has not been well studied. Because of this, it may be useful to explore the relative merits of orchiectomy plus an aromatase inhibitor compared with the combination of GnRH analog plus an aromatase inhibitor.

Although randomized comparisons may not be feasible due to the low number of male breast cancer patients, it may be possible to address this research question in a surrogate tumor type such as prostate cancer, and such plans are already under way in one of our centers.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Beware of Amenorrhea During Tamoxifen: It May Be a Wolf in Sheep's Clothing

TO THE EDITOR: With great interest we read the review of Walshe et al[1] on the beneficial prognostic effects of developing amenorrhea after chemotherapy for breast cancer in premenopausal women. In their summary of the literature about the influence of tamoxifen on chemotherapy-induced amenorrhea, five studies are cited that found higher rates of amenorrhea after the addition of tamoxifen after adjuvant chemotherapy.[2-6]

In evaluating the effect of amenorrhea on breast cancer survival in these retrospective studies, menopausal status and amenorrhea are not defined in a consistent manner, which may even be more erratic and deceiving during tamoxifen use. We would like to underscore this with the data from a study on ovarian function during tamoxifen in 114 young breast cancer patients ($\leq$ 56 years of age) by performing serial transvaginal ultrasonography and serum follicle stimulating

hormone and estradiol.[7] Menopausal status after chemotherapy was defined by serum estradiol levels of more than 0.10 nmol/L and follicle stimulating hormone ≤ 30.0 U/L, irrespective of the presence or absence of menses. Patients treated with high-dose chemotherapy (n = 51) all developed amenorrhea and a postmenopausal hormone status. After standard-dose chemotherapy in 63 patients, 21 developed amenorrhea. In 27 patients with premenopausal hormone levels, 19 patients (70%) developed ovarian cysts, despite amenorrhea in 12. Patients with ovarian cysts had much higher serum estradiol levels (2.18 nmol/L; standard deviation, 1.31; $P < .0001$) than patients without cysts (0.15 nmol/L; standard deviation, 0.20). Women with ovarian cysts and high estradiol levels often reported a disappearance of hot flashes during amenorrhea, indicating an estrogenic effect overriding tamoxifen (unpublished data).

Therefore, we would like to stress the fact that especially during tamoxifen, amenorrhea may falsely suggest ovarian failure, hiding the presence of hyperactive ovaries due to a positive feedback mechanism, which is the opposite from the ovarian failure caused by chemotherapeutic agents. During tamoxifen, amenorrhea may actually be a wolf in sheep's clothing. The disappearance of flushes during amenorrhea may indicate the presence of hyperactive ovaries with too high estrogen levels. Apart from the epidemiologic and prognostic issues mentioned earlier, this may be particularly of concern when patients, apparently suffering from permanent ovarian failure, are subsequently put on aromatase inhibitors, which will be ineffective in this situation and even may lead to unwarranted pregnancies, while in fact we are dealing with overactive ovaries.

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In Reply: We thank Mourits et al for further emphasizing that amenorrhea, which occurs after chemotherapy and/or tamoxifen in premenopausal women, may indeed be reversible. We agree that there is no consensus on the definition of drug-induced amenorrhea. Mouritis et al also reiterate that drug-induced amenorrhea is not always synonymous with lack of ovarian function, and correctly point out that tamoxifen may cause an increase in estrogen concentration and thus contribute to ovarian cysts.[1,2] As we stated in our review, it is not clear how tamoxifen induces increases in estradiol or why there may be increased rates of amenorrhea.[3] We will provide further clarification herein on the endocrine changes encountered during tamoxifen therapy.

Multiple small studies describing the hormone changes associated with tamoxifen therapy note increases in estradiol levels in premenopausal women.[4-7] In one study, 2 to 3 months of tamoxifen in healthy volunteers resulted in increased estradiol levels, but did not suppress luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels.[5] A second study evaluated the levels of estradiol and gonadotropins in women who received 4 to 72 months of adjuvant tamoxifen and also in control subjects. The women taking tamoxifen continued to menstruate, and had increased estradiol levels and stable LH and FSH levels compared with controls.[7]

Endocrine changes after the combination of chemotherapy and tamoxifen have also been studied. One particular study evaluated the impact of cyclophosphamide, methotrexate, and fluorouracil (CMF), CMF plus prednisone (CMFP), and CMFP plus tamoxifen (CMFPT) on ovarian and adrenal function in premenopausal breast cancer patients.[8] Women that achieved amenorrhea after CMF or CMFP had decreased estradiol levels and elevations of FSH and LH. Women receiving CMFPT who achieved amenorrhea also had decreased estradiol levels, but did not have elevations of LH or FSH. In contrast, women who received CMFPT but did not achieve amenorrhea had elevated estradiol levels.

Another study compared hormone levels in premenopausal patients who were treated with CMF, CMF and concurrent tamoxifen, or tamoxifen alone before and after stimulation with gonadotropin releasing hormone (GnRH) and thyrotropin releasing hormone.[9,10] Estradiol levels were decreased and FSH and LH were increased in women who achieved amenorrhea with CMF and tamoxifen, while gonadotropin elevation was less pronounced in the group that received tamoxifen alone. Gonadotropin response to GnRH was suppressed in women who achieved amenorrhea after CMF. However, in women who received tamoxifen alone or concurrently with CMF who continued to menstruate, estrogen levels increased and levels of FSH and LH were unchanged. After GnRH and thyrotropin releasing hormone administration, the FSH and LH levels were markedly elevated. This exaggerated response of FSH and LH to GnRH in the presence of tamoxifen suggests that tamoxifen may block the hypothalamic estrogen receptors and interfere with normal feedback regulation of ovarian steroidogenesis.