Estrone Sulphate, FSH, and Testosterone Levels in Two Male Breast Cancer Patients Treated with Aromatase Inhibitors

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INTRODUCTION

The role of aromatase inhibitors (AIs) in male breast cancer patients is still unknown.

In preclinical models, administration of these drugs was associated with significant increases in follicle-stimulating hormone (FSH) and testosterone and no change in estradiol (E_2) levels [1], whereas in healthy men administration of AIs causes a significant decrease in E_2 but an increase in FSH, luteinizing hormone, and testosterone [2]. Recently, Doyen et al. [3] reported on the largest experience of the efficacy of AIs in male breast cancer patients and their impact on E_2 levels. In that retrospective analysis, AIs were administered to 15 metastatic patients and showed acceptable activity, with two complete responses (13%), four partial responses (13%), and two cases of disease stabilization (13%). All assessable patients ($n = 6$) had E_2 levels less than the lower limit of the assay during AI treatment.

These results demonstrate that AIs are active in male

breast cancer and show a significant reduction in E_2 levels. FSH and testosterone levels were not assessed.

METHODS

We report two cases of male breast cancer treated with AIs in which we determined, prospectively, estrone sulphate (an estrogen metabolite), testosterone, and FSH levels.

The first patient was a 63-year-old man with metastatic breast cancer. He was diagnosed with a right-side locally advanced ductal invasive carcinoma that was stage cT4 N2 and estrogen and progesterone receptor–positive and human epidermal growth factor receptor (HER)-2[−] by immunohistochemistry. Instrumental staging revealed multiple lung and thoracic lymph nodes metastases. He received first-line chemotherapy containing anthracycline and taxanes. During that treatment, he developed a pulmonary thromboembolism. For this reason, chemotherapy was stopped and letrozole was begun. Letrozole was interrupted

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Table 1. Estrone sulphate, follicle-stimulating hormone (FSH), and testosterone levels at baseline and after 6 weeks of aromatase inhibitor treatment

	Estrone sulfate (pg/ml)			Testosterone (pg/ml)			FSH (MIU/ml)		
	Basal	6 wks	% decrease	Basal	6 wks	% increase	Basal	6 wks	% increase
Patient #1	472	109	−77%	6,650	8,570	+29%	10.8	33.9	+214%
Patient #2	306	63	−79%	1,040	1,320	+21%	10.8	19.6	+81%

after 3 months as a result of lung disease progression and second-line chemotherapy with vinorelbine was begun.

The second patient was a 64-year-old man diagnosed with early breast cancer. He was treated with a right mastectomy for a stage pT2N1a invasive ductal carcinoma that was estrogen and progesterone receptor–positive and HER-2⁺ (3+) by immunohistochemistry. He received adjuvant chemotherapy containing anthracyclines and taxanes and began adjuvant trastuzumab. We prescribed adjuvant tamoxifen, but after <1 year, patient developed a detached retina so we switched tamoxifen with anastrozole. The patient is still receiving adjuvant anastrozole.

These two patients received an AI because they developed two clinical conditions (pulmonary thromboembolism and detached retina) for which tamoxifen might not be safe. Estrone sulphate, testosterone, and FSH levels were assessed prospectively in order to add a gonadotropin-releasing hormone analog if estrone sulphate reduction was not achieved [4].

Plasma samples were obtained before the beginning of AI treatment and 6 weeks thereafter (i.e., at concentration steady state levels of AIs). FSH and testosterone were evaluated by a commercially available electrochemiluminescence immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Estrone sulphate was evaluated by a commercially available radioimmunoassay kit (DSL-5400; Diagnostic Systems Laboratories Inc., Webster, TX) after a nonchromatographic cleaning of samples from dehydroepiandrosterone sulphate [5]. Activity was measured using a γ scintillation counter (Cobra II Autogamma; Canberra-Packard Central Europe GmbH, Schwandorf, Austria). Plasma estrone sulphate is produced by sulfatation of circulating estrone, and estradiol, estrone, and estrone sulphate levels are in equilibrium [6]. Thus, inhibition of peripheral aromatase causes a similar drop in all three plasma estrogens.

RESULTS

Table 1 shows estrone sulphate, FSH, and testosterone levels at baseline and after 6 weeks of AI treatment.

Assuming that circulating estrogen levels in the male do not change significantly with age [7], basal plasma estrone

sulphate concentrations in the two men were similar to data previously reported in the literature [5, 8, 9].

We observed an increase in FSH levels but a marked decrease in estrone sulphate levels in both patients. Testosterone levels increased slightly.

CONCLUSIONS

In animals and healthy men, AI treatment leads to an increase in both FSH and testosterone [10]. Because testosterone is the substrate for aromatase in estrogen synthesis, a lower suppression of estrogens by AIs can be achieved in men. On this basis, it was hypothesized that gonadotropin-releasing hormone analogs could inhibit the feedback loop to the hypothalamus and pituitary glands, leading to better suppression of estrogen by AIs [4]. However, chronic administration of a gonadotropin-releasing hormone analog in men is associated with some undesirable side effects, such as a decrease in libido, impotence, hot flushes, gynecomastia [11], and osteoporosis [12].

Our data confirm that of Mauras et al. [2]. We observed an increase in FSH (from about two- to threefold the basal values) and an increase in circulating testosterone levels of about 20%–30%. Suppression of estrogen synthesis after 6 weeks of AI treatment was high (near 80%) and comparable with that observed in postmenopausal women treated with letrozole [13].

Therefore, the increase in FSH and circulating testosterone levels did not seem to influence AI activity. This could be explained by the fact that estrogen produced by the testes, not susceptible to aromatase inhibition and stimulation by FSH, accounts for only 20% of circulating estrogen [7] and by the high activity of AIs in inhibiting androgen aromatization to estrogens, which counteracts the weak increase in circulating testosterone.

Our biochemical data show high activity of AIs in estrogen suppression in men affected by breast cancer as well, despite the increase in FSH and circulating testosterone levels, and do not support the need for gonadotropin-releasing hormone analogs in combination with AIs, as previously suggested [4].

AUTHOR CONTRIBUTIONS

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