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Aromatase inhibition in male breast cancer patients: biological and clinical implications

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Background: The role of aromatase inhibitors (AIs) and their impact on estradiol (E_2) levels remain unknown in male breast cancer (MBC) patients.

Patients and methods: MBC patients with metastatic disease and those treated with AIs were selected from the breast cancer database of the Centre Antoine-Lacassagne (Nice, France). Sex hormone levels were retrospectively assessed on serum samples from our institutional serum bank.

Results: Fifteen patients entered the study. Two patients (13%) had complete response, four patients (27%) had partial response, two patients (13%) had stable disease and seven patients (47%) had progressive disease. The median progression-free survival and overall survival were 4.4 months [95% confidence interval (CI) 0.1–8.6] and 33 months (95% CI 18.4–47.6), respectively. All assessable patients ($n = 6$) had E_2 levels less than the lower limit of the assay during AI treatment. Among them, three had partial response, one had stable disease and two had progressive disease. A large increase in follicle-stimulating hormone, luteinizing hormone and E_2 levels was observed in one responding patient at progression.

Conclusions: AIs are active in MBC patients. This activity is correlated with a significant reduction in E_2 levels. Secondary resistance is in part related to a deleterious feedback loop resulting in a significant increase in substrate for aromatization.

Key words: anastrozole, aromatase inhibitors, exemestane, letrozole, male breast cancer

introduction

Male breast cancer (MBC) is a rare tumor that accounts for <1% of breast cancers, although its incidence has increased by 26% over the last 25 years. Because this disease is rare, treatment recommendations are largely derived from results of trials in female patients. Hormonal therapy is the mainstay of treatment for advanced disease. Indeed, estrogen receptor (ER) and progesterone receptor (PR) positivity has been reported in >90% of cases. The huge therapeutic effect of bilateral orchiectomy in the management of metastatic disease in men was described for the first time in 1942. Although surgical ablative therapies such as orchiectomy, adrenalectomy and hypophysectomy have been used effectively to control metastatic breast cancer in male patients, tamoxifen has become the first hormonal therapy of choice. Indeed, the use of tamoxifen avoids surgical morbidity, resulting from ablative procedures, is more acceptable to men than orchiectomy and was associated with response rates ranging from 25% to 80% in several retrospective series. Although, several studies have shown the superiority of third-generation aromatase inhibitors (AIs) (anastrozole, letrozole and exemestane) over tamoxifen in menopausal women with advanced breast cancer, the role of such molecules remains largely unknown in male patients.

We report here the largest experience about the efficacy of AIs in MBC patients with advanced disease and their impact on estradiol (E_2) and testosterone levels.

patients and methods

Patient cases were selected from our institution database on the basis of the following criteria: (i) histologically confirmed breast cancer, (ii) metastatic disease with at least one measurable or assessable nonmeasurable lesion, (iii) ER- and/or PR-positive primary and/or metastatic tumors, (iv) availability of complete clinical and histological data, (v) evidence of progressive disease at initiation of AI and (vi) receipt of at least 1 month of treatment with nonsteroidal (anastrozole and letrozole) or steroidal (exemestane) AI. Patients who received concomitant chemotherapy and/or radiotherapy were excluded from the analysis. Clinical and histological characteristics of all patients were obtained from medical records and entered prospectively into our institutional clinical database. Tumor response was assessed according to RECIST. Complete response was defined by disappearance of all target lesions. Partial response was defined by a decrease of at least 30% in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum of LD. Progressive disease was defined by an increase of at least 20% in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started

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or the appearance of one or more new lesions. Stable disease was defined by a shrinkage not sufficient to qualify for PR or an increase not sufficient to qualify for PD, taking as reference the smallest sum LD since the treatment started. In patients with measurable disease, progression was determined by RECIST. In patients without measurable lesions, progression was defined as development of new lesions or evident progression of existing lesions.

Sex hormone levels were retrospectively assessed on serum samples from our institutional serum bank. E_2 level was measured by direct double-antibody radioimmunoassays (Pasteur Cerba, Saint Ouen l'Aumone, France), whereas follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were measured by electrochemiluminescent immunoassay (Pasteur Cerba). The normal ranges for each hormones were as follows: E_2 = 80–120 pmol/l, FSH = 1.5–12.4 mIU/ml and LH = 1.7–8.6 mIU/ml. Dosages were carried out on serum samples drawn before AI introduction and during AI treatment on the basis of serum sample availability for each patient.

The statistical analysis of baseline demographics and the clinical outcome is determined on the basis of all data available up to the cutoff date of 30 August 2008. Overall survival (OS) was defined as the interval between initiation of AI therapy and time of death. Progression-free survival (PFS) was defined as the interval between initiation of AI therapy and time of progression or death from any cause.

results

patients

Fifteen patients, treated between 1999 and 2007, entered the study. Median age was 68 years (range 39–85) (Table 1). Seven patients received previous lines of hormonal therapy (median = 1, range 1–4) and three patients a previous line of chemotherapy before the introduction of AIs. Ten patients (67%) had bone and/or nodes and/or skin metastases and five patients (33%) had visceral metastases.

efficacy

The best response was complete response in two patients (13%), partial response in four patients (27%), stable disease in two patients (13%) and progressive disease in seven patients (47%) (Table 1). The median duration of objective response was 11.6 months [95% confidence interval (CI) 7.6–15.5]. At the last follow-up, eight patients (53%) had died and seven (47%) were still alive. The median PFS and OS were 4.4 months (95% CI 0.1–8.6) and 33 months (95% CI 18.4–47.6), respectively. The 1-year PFS and OS rates were 20% (95% CI 9.7% to 30.3%) and 84.6% (95% CI 74.6% to 94.6%), respectively.

E_2 levels

Six patients had available samples for E_2 level analysis. All assessable patients had E_2 levels less than the lower limit of the assay during AI treatment. Such levels were not detectable in four cases (<20 pmol/l). Among these six patients, three had partial response, one had stable disease and two had progressive disease. Two of six patients had available samples at progression (patients 1 and 2). One patient (patient 1) had a large increase in E_2 level, which was associated with an increase in FSH (27.5 mIU/ml) and LH (13.6 mIU/ml) levels. The other patient (patient 2) had still undetectable E_2 level at progression.

discussion

Since the hormonal environment in male patients differs from that in female patients, the role of AIs in male patients is not as clear as it appears in female ones. In men, ~80% of circulating estrogens are derived from peripheral aromatization of

Table 1. Patients' characteristics and correlation between E_2 level and AI efficacy

	Age (years)	Metastases	Previous lines of treatment	Efficacy	E_2 level during AI treatment	Type of AI	Duration of AI (weeks)
Patient 1	68	Lung, bone, nodes	2	PR	<20 pmol/l, 330 pmol/l at progression	Exemestane	86
Patient 2	55	Bone	0	PR	<20 pmol/l (<20 pmol/l at progression)	Exemestane	119
Patient 3	64	Nodes, skin	5	CR	NA	Letrozole	54
Patient 4	70	Bone	0	PR	NA	Exemestane	31
Patient 5	44	Lung, nodes	1	CR	NA	Letrozole	406
Patient 6	72	Lung, bone, nodes	0	PR	40 pmol/l	Anastrozole	42
Patient 7	84	Bone	0	SD	NA	Anastrozole	50
Patient 8	60	Bone	2	SD	<20 pmol/l	Exemestane	15
Patient 9	41	Lung, nodes	1	PD	NA	Anastrozole	14
Patient 10	52	Bone, nodes	0	PD	NA	Letrozole	17
Patient 11	60	Nodes	0	PD	NA	Letrozole	19
Patient 12	49	Bone	0	PD	NA	Letrozole	16
Patient 13	62	Bone	3	PD	30 pmol/l	Anastrozole	13
Patient 14	70	Nodes	1	PD	<20 pmol/l	Anastrozole	9
Patient 15	38	Lung, nodes	0	PD	NA	Exemestane	10

Estradiol normal range = 80–180 pmol/l.

AI, aromatase inhibitor; PR, partial response; CR, complete response; NA, not available; SD, stable disease; PD, progressive disease.

testicular and adrenal androgens, with direct production from the testes accounting for the remaining 20%. Several studies carried out in healthy men have demonstrated that administration of nonsteroidal AIs causes a significant decrease in plasma E_2. However, data about the impact of AIs on E_2 plasma levels in MBC patients and their clinical efficacy are almost nonexistent [1–5]. Our results have demonstrated that aromatase inhibition leads to a significant decrease of E_2 level in MBC patients. However, E_2 levels remained detectable (≥20 pmol/l) in two of six patients. In postmenopausal women, anastrozole or letrozole suppresses by 80%–90% E_2 levels, which therefore become undetectable by standard assays [6]. However, baseline E_2 levels are higher in men than in postmenopausal women because of a higher level of peripheral androgens [7]. Moreover, AIs are not able to inhibit the testicular production of estrogen, which account for 20% of the circulating estrogen [8].

In healthy men, fadrozole [9], letrozole [10] and anastrozole [11] hydrochloride caused a significant increase of LH and FSH. This may be the consequence of a potential deleterious feedback loop that could lead to an increase in substrate for aromatization. The 'feedback loop' hypothesis is supported by findings observed in patient 1 who experienced first a partial response under exemestane treatment but then developed secondary resistance. Indeed, at progression, this patient had an increase in E_2 levels, which was associated with increase in LH and FSH. The potential existence of a feedback loop indicates that suppression of estrogen production in male patients by monotherapy using AIs may be suboptimal. This represents a good rationale to investigate the clinical activity of AIs in combination with the analogue LH–releasing hormone. Interestingly, patient 2 had still undetectable E_2 levels at progression indicating alternative mechanisms of secondary resistance to AI, such as tumor hormone independence [12] or increased intratumoral aromatase [13].

Despite the limitations of a retrospective analysis, our results demonstrate that AIs are active in MBC patients and that this activity is correlated with a significant reduction in E_2 levels. Further investigations are needed to explore the acquired mechanisms of resistance to AIs in MBC patients. In this regard, the Southwest Oncology Group should be commended for having planned to bank tissue and serum samples from patients enrolled in the S0511 trial, which evaluated the combination of anastrozole and goserelin in men with hormone receptor-positive metastatic breast cancer and from which the results are still awaited.

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