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Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series

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Background: Data regarding the safety and effectiveness of aromatase inhibitors (AIs) as monotherapy or combined with gonadotropin-releasing hormone (GnRH) analogue in male breast cancer are scarce.

Methods: In this retrospective chart review, cases of male breast cancer patients treated with AIs with or without a GnRH analogue were evaluated.

Results: Twenty-three men were included into this case series. Aromatase inhibitors in combination with or without a GnRH analogue were given as first-line therapy in 60.9% and as second-line therapy in 39.1% of patients, respectively. All patients had visceral metastases, whereas in five of them bone lesions coexisted. In all cases AIs were tolerated well, and no case of grade 3 and 4 adverse events was reported. A partial response was observed in 26.1% of patients and stable disease in 56.5%. Median overall survival (OS) was 39 months and median progression-free survival (PFS) was 13 months. Regarding OS and PFS, no significant effects of GnRH analogue co-administration or type of AI were noted.

Conclusion: Our study shows that AIs with or without GnRH analogues may represent an effective and safe treatment option for hormone-receptor positive, pretreated, metastatic, male breast cancer patients.

Male breast cancer is an uncommon malignancy, accounting approximately for only 1% of all breast cancer cases (NCCN Clinical Practice Guidelines in Oncology, 2012). The rarity of this disease has resulted in a limited amount of clinical data; indeed, very few clinical trials were conducted specifically in male patients and, conclusions concerning treatment strategies therefore have been generally drawn from trials conducted in female patients. Consequently, men with breast cancer are treated similarly to women, except for hormonal treatment (NCCN Clinical Practice Guidelines in Oncology, 2012). More specifically, tamoxifen is still the golden standard of adjuvant endocrine treatment in male breast cancer and has a key role in the metastatic setting as well (NCCN Clinical Practice Guidelines in Oncology, 2012; Eggemann *et al*, 2013).

Unlike tamoxifen, which acts as elective oestrogen receptor modulator, aromatase inhibitors (AIs) prevent the conversion of androstendione to 17β-estradiol (Jordan *et al*, 2011) Data from large randomised clinical trials in women have demonstrated a reduced risk of breast cancer recurrence with 5 years of adjuvant AIs as compared with 5 years of tamoxifen as adjuvant treatment (Bonneterre *et al*, 2000; Nabholtz *et al*, 2000; Mouridsen *et al*, 2001; Cuzick *et al*, 2010; Regan *et al*, 2011; Bliss *et al*, 2012). Hence, AIs are currently considered the treatment of choice for postmenopausal women with hormone-receptor (HR) positive breast cancer

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(Aebi *et al*, 2011; NCCN Clinical Practice Guidelines in Oncology, 2012); their role in male breast cancer, however, remains elusive.

In preclinical models, administration of AIs was associated with significant increases in the respective levels of follicle-stimulating hormone (FSH) and testosterone, whereas and no change in oestradiol (E2) levels was observed (Turner *et al*, 2000; Bighin *et al*, 2010). In healthy men, on the other hand, the administration of AIs caused a significant decrease in E2 levels; at the same time, an increase in levels of FSH, luteinising hormone, and testosterone was observed (Mauras *et al*, 2000; Bighin *et al*, 2010). Notably, the increase in testosterone levels may overcome the effect of aromatase inhibition by flooding the enzyme pathway with substrate, eventually resulting in only modest reduction of serum oestrogen levels and thereby limiting the clinical activity of AIs in men (White *et al*, 2011; Eggemann *et al*, 2013). Combination therapy with gonadotropin-releasing hormone (GnRH) analogues, that is, goserelin acetate effectively reduces the excess substrate levels, and may therefore maximise the effect of aromatase inhibition, suggesting that such a combination may be more effective than AIs alone in metastatic male breast cancer patients (Giordano and Hortobagyi, 2006; Soon Wong *et al*, 2007; Onami *et al*, 2010).

Data regarding the safety and effectiveness of AIs as monotherapy or combined with GnRH analogues in metastatic male breast cancer are scarce. Our retrospective study, the largest henceforth, therefore evaluated efficacy and safety of AIs with or without goserelin in metastatic male breast cancer cases.

MATERIALS AND METHODS

The study population was based on male patients with metastatic breast cancer who have been treated with AIs with or without a GnRH analogue. Eligible patients were selected from the Comprehensive Cancer Center of Vienna, Department of Medicine I/Division of Oncology, Vienna, Austria, from the 1st Propaedeutic Surgical Department of Hippocrateio Hospital, University of Athens, Athens, Greece and from the Department of Clinical Therapeutics, Alexandra Hospital, University of Athens, Greece. Patients were managed by dedicated teams of breast cancer specialists at these academic breast centres. The decision for further endocrine treatment after standard therapy with tamoxifen was taken in an interdisciplinary tumour board. Of note, the use of AI with or without a GnRH analogue, in each patient, was a medical decision taken independently of the presence of symptoms, visceral metastases or other clinical parameters. Patients' medical records were reviewed and information regarding demography, pathology, and outcome was obtained; data of all patients were entered prospectively into the respective institutional clinical databases.

In all cases, an oral AI (either exemestane 25 mg, or letrozole 2.5 mg or anastrozole 1 mg) was administered daily, either alone or combined with a GnRH analogue (goserelin acetate 3.6 mg on day 1 in four weekly intervals). Treatment was continued until disease progression or unacceptable toxicity.

Exclusion criteria were the following: (i) patients who had received AIs in the adjuvant setting, (ii) patients with HER2-positive breast tumours, (iii) patients who received concomitant chemotherapy, trastuzumab and/or radiotherapy (iv) previous GnRH analogue administration, (v) patients without at least one measurable or assessable non-measurable lesion and (vi) oestrogen receptor (ER)- and progesterone receptor (PgR)-negative primary and/or metastatic breast cancer.

In cases where more than one agent of the class of AI was administered consecutively, data regarding the first AI was included into the analysis. In patients with measurable disease, response was determined by RECIST 1.1 criteria. Fisher's exact test was performed to assess whether co-administration of goserelin, as well as the type of administered AI (that is, irreversible steroidal inhibitor (exemestane) or a non-steroidal inhibitor (anastrozole and letrozole)), were associated with response rates.

Overall survival (OS) was defined as the interval between initiation of AI therapy and time of death, whereas progression-free survival (PFS) was defined as the interval between initiation of AI therapy and time of progression or death of any cause. Kaplan–Meier survival curves were estimated for the graphical presentation of results. Log-rank test for the equality of survivor functions was performed in order to assess whether co-administration of goserelin as well as the type of administered AI was associated with differences in terms of OS and PFS.

Statistical analysis was performed with STATA 11.1 software (Stata Corp., College Station, TX, USA). Written informed consent was obtained by all subjects participating in the study. The study is in accordance with the Helsinki Declaration and has been approved by the local institutional review boards.

RESULTS

Twenty-three men aged 53–76 years (64.4 ± 6.5; mean ± s.d.) were included into this case series. Patients' characteristics are depicted in Table 1. All of them had undergone modified radical mastectomy. Eighteen of them (78.3%) were diagnosed with invasive ductal carcinoma, whereas the remaining five (21.7%) had infiltrative lobular carcinoma. The majority of patients presented with high grade neoplasms (grade 3: 47.8%; grade 2: 43.5%; grade 1: 8.7%). The ER Allred score varied between 4 and 8; the mean score was 6.61 ± 1.20. The Allred score for PR varied between 0 and 7; the mean score was 4.91 ± 1.81; all patients were HER2 negative, whereas ki-67 positivity (%) ranged between 10–60% (mean 31.0 ± 13.8%). None of the patients included into this analysis was diagnosed with metastatic disease at first presentation.

The majority of patients received letrozole or anastrozole (82.6%); the remainders were treated with exemestane (17.4%). All patients except for one had received radiotherapy as part of their adjuvant treatment; the predominant adjuvant chemotherapy regimen was a combination of anthracyclins and taxanes (56.5%).

Adjuvant hormonal treatment was administered in 92.9% of cases; one patient did not consent. Of note, all patients had received tamoxifen beforehand. Aromatase inhibitors were given as monotherapy in 26.1% of patients, whereas in combination with goserelin acetate in 73.9% of patients. Aromatase inhibitors in combination with or without goserelin acetate were given as first-line therapy in 14 (60.9%) patients and as second-line therapy in nine (39.1%) patients. All patients had visceral metastases, whereas in five of them bone lesions coexisted. In all cases, AI with or without goserelin acetate was tolerated well, without grade 3 and 4 adverse events being reported.

Regarding best response, partial response (PR) was noted in 6 (26.1%) patients, stable disease (SD) in 13 (56.5%) patients, whereas progressive disease (PD) was observed in 4 (17.4%) patients. The GnRH analogue co-administration was not associated with response rates, as the PD : SD : PR ratio among patients receiving GnRH analogue and those who did not was 17.7% : 64.7% : 17.7% and 16.7% : 33.3% : 50.0%, respectively, ($P = 0.306$, Fisher's exact test). Similarly, steroidal inhibitor administration was not associated with response rates, as the PD : SD : PR ratio among patients receiving irreversible steroidal and non-steroidal inhibitors was 25.0% : 75.0% : 0.0% and 15.8% : 52.6% : 31.6%, respectively, ($P = 0.463$, Fisher's exact test).

Median OS was 39 months and median PFS was 13 months; corresponding Kaplan–Meier survival estimates are presented in

Table 1. Description of the study sample

Continuous variables	mean ± s.d.
Age (years)	64.4 ± 6.5
ER expression (Allred score)	6.61 ± 1.20
PgR expression (Allred score)	4.91 ± 1.81
Ki-67 (%)	31.0 ± 13.8
Categorical and ordinal variables	**N (%)**
Histological type	
Invasive ductal carcinoma	18 (78.3)
Infiltrative lobular carcinoma	5 (21.7)
Grade	
1	2 (8.7)
2	10 (43.5)
3	11 (47.8)
Adjuvant radiotherapy	
Yes	22 (95.6)
No	1 (4.4)
Adjuvant chemotherapy	
Anthracyclin based	5 (21.7)
Taxane based	3 (13.0)
Anthracyclin plus taxane based	13 (56.5)
Unknown	1 (4.4)
No	1 (4.4)
Type of AI administered	
Non-steroidal (letrozole or anastrozole)	19 (82.6)
Steroidal (exemestane)	4 (17.4)
Co-administration of goserelin	
Yes	17 (73.9)
No	6 (26.1)
Line of treatment	
First	14 (60.9)
Second	9 (39.1)
Best response	
PD	4 (17.4)
SD	13 (56.5)
PgR	6 (26.1)

Abbreviations: AI = aromatase inhibitor; ER = oestrogen receptor; PD = progressive disease; PgR = progesterone receptor; SD = stable disease.

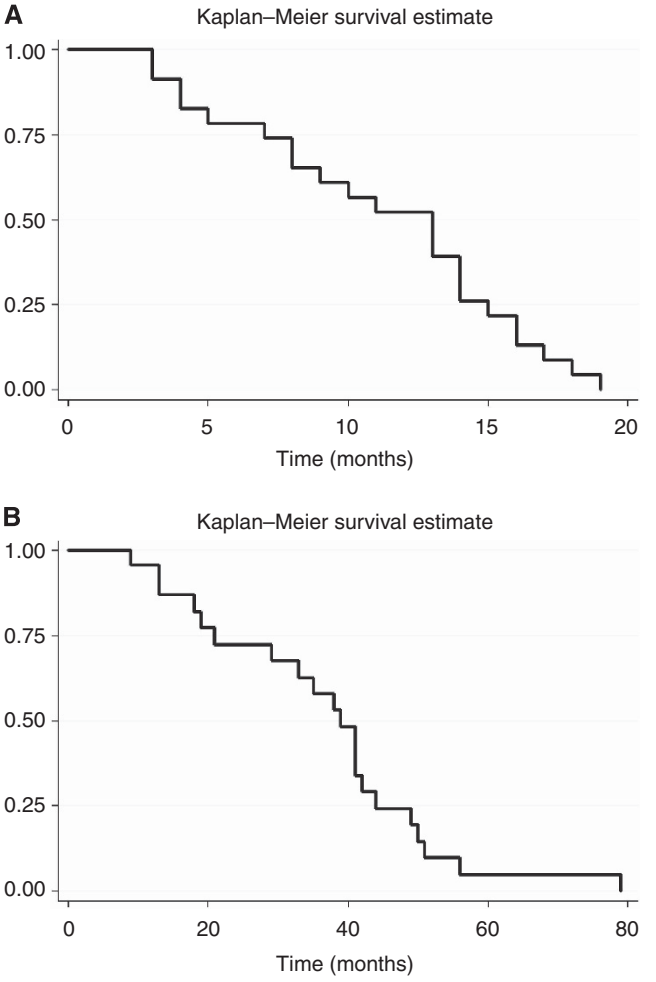

Figure 1. Kaplan–Meier survival curves regarding. (**A**) OS and (**B**) PFS.

Figures 1A and B, respectively. Regarding OS, no significant effects of goserelin co-administration (log-rank $\chi^2(1) = 0.38$, $P = 0.536$) or type of AI agent (log-rank $\chi^2(1) = 1.03$, $P = 0.310$) were noted. Similarly, goserelin co-administration (log-rank $\chi^2(1) = 0.04$, $P = 0.850$) and type of AI (log-rank $\chi^2(1) = 0.02$, $P = 0.875$) were not associated with PFS.

DISCUSSION

Our study shows that AIs with or without GnRH analogues may represent an effective and safe treatment option for HR-positive, pretreated, metastatic, male breast cancer patients. It is possible that the high rate of responses achieved in our patient population may be attributed to the combination of AI with GnRH analogue. Moreover, the combination of an AI with a GnRH analogue in theory offers the added advantage of inhibiting the aromatisation of androgens to estrogens, while inhibiting the positive feedback loop to the hypothalamus/pituitary glands by the effect of goserelin acetate. This effect is of great importance taking into consideration that hormonal therapy is the mainstay of treatment in metastatic male breast cancer as men have a high rate of HR positivity, and thus excellent response rates to hormonal manipulation (Stalsberg *et al*, 1993; Rayson *et al*, 1998; Onami *et al*, 2010); nevertheless, the small sample size did not allow for the robust testing of such a hypothesis, and thus larger studies are needed in order to fully elucidate the role of goserelin in male breast cancer.

In male breast cancer, surgical hormonal ablative procedures were attempted initially, and in 1941, Farrow and Adair (1942) reported on the efficacy of orchiectomy. Other ablative techniques such as adrenalectomy and hypophysectomy were explored as well, with overall response rates of >50%. However, these techniques are now rarely used and have been substituted by medical hormonal treatment. Agents such as androgens, antiandrogens, steroids, estrogens, progestins and tamoxifen have shown promising activity, and are psychologically more acceptable to the majority of men than orchiectomy (Giordano *et al*, 2002; Arriola *et al*, 2007; White *et al*, 2011). Currently, tamoxifen is the cornerstone of hormonal treatment for male breast cancer, although the definition of this standard results from relatively small retrospective studies or is extrapolated from trials conducting

in female breast cancer patients (Kantarjian *et al*, 1983; White *et al*, 2011). The use of fulvestrant in male breast cancer was proposed owing to their success in females, with a few published case series showing promising results in men as well (de la Haba Rodríguez *et al*, 2009; Masci *et al*, 2011; Zagouri *et al*, 2013).

The use of AIs in male breast cancer is well tolerated (Visram *et al*, 2010), but remains controversial. Initial case series have disappointingly shown negative or equivocal results; in a series of five patients, no objective response to anastrozole was observed (Giordano *et al*, 2002). Interestingly, however, there have been three individual cases of response to letrozole (Italiano *et al*, 2004; Zabolotny *et al*, 2005; Arriola *et al*, 2007), while Doyen *et al* (2010) reported promising results (CR: 13%; PR: 27% and SD: 13%), indicating relevant clinical activity of AIs in male breast cancer patients. In this study, median PFS and OS were 4.4 months (95% confidence interval (CI) 0.1–8.6) and 33 months (95% CI 18.4–47.6), respectively, (Doyen *et al*, 2010). In addition, the activity of letrozole was correlated with a significant reduction in E(-2-) levels, while secondary resistance was in part related to a deleterious feedback loop resulting in a significant upregulation of testosterone, thereby increasing substrate levels for aromatisation (Doyen *et al*, 2010). Hence, it was speculated that the combination of an AI with a GnRH analogue provide superior results.

Our study confirms that AIs combined with a GnRH analogue are active in male breast cancer, with a clinical benefit rate (CR, PR and s.d. $\geqslant$6 months) reported equal to 82.3%. Our observation is in accordance with data published in female breast cancer patients receiving AIs in metastatic setting (ORR ranging from 49% to 59%; time to treatment progression ranging from 8.3 to 11.1 months; Bonneterre *et al*, 2000; Nabholtz *et al,* 2000; Mouridsen *et al*, 2001). Moreover, our data are in accordance with the data published by (Giordano and Hortobagyi, 2006), on two male breast cancer patients treated with leuprolide acetate plus AIs. Still, results of patients receiving the combination of AIs and GnRH analogues were not significantly superior as compared with patients receiving AIs alone in our study. Therefore, it is obvious that no firm conclusion can be drawn, given the limited patient number as well as the limited amount of available literature. In addition, the main limitation of our study is its retrospective design; unfortunately, the SWOG-S0511 trial –a small, phase II trial in male breast cancer patients with recurrent or metastatic disease, in which goserelin was administered combined with anastrozole (ClinicalTrials.gov; ID: NCT00217659)– was closed prematurely owing to poor accrual (Sousa *et al*, 2013). Moreover, a randomised trial evaluating AIs in metastatic male breast cancer with or without a GnRH analogue is more than warranted.

Despite the limitations of a retrospective analysis, our results demonstrate that AIs in combination with or without goserelin may represent an effective and safe treatment option for HR-positive, pretreated, metastatic, male breast cancer patients who had progressed on tamoxifen. Further trials and large case series focused on male breast cancer and AI with or without goserelin seem mandatory to draw any firm conclusion.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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