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Rapid communication

Is there a benefit by the sequence anastrozole–formestane for postmenopausal metastatic breast cancer women?

Paolo Carlini [a,*], Gianluigi Ferretti [a], Serena Di Cosimo [a], Elvira Colella [a], Riccardo Tonachella [a], Adriana Romiti [b], Silverio Tomao [b], Antonio Frassoldati [c], Paola Papaldo [a], Alessandra Fabi [a], Enzo Maria Ruggeri [a], Francesco Cognetti [a]

[a] *Department of Medical Oncology, Regina Elena Cancer Institute, Via Elio Chianesi 53, Rome, Italy*
[b] *Department of Experimental Medicine and Pathology, University of "La Sapienza", Rome, Italy*
[c] *Division of Medical Oncology, University of Modena, Modena, Italy*

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Abstract

To explore the different sequence interactions between reversible non-steroidal (anastrozole, ANZ and letrozole, LTZ) and non-reversible steroidal aromatase inhibitors (formestane, FOR and exemestane, EXE), we evaluated the clinical benefit (CB) in postmenopausal breast cancer patients, who had previously received anastrozole and subsequently formestane. In 19 out of 21 patients (90.5%), a clinical benefit response was achieved by anastrozole, with a median duration of 12 months. Out of the 21 women progressing on anastrozole, 12 achieved stable disease (SD) $\geq$ 6 months by formestane only. The overall clinical benefit was 66.5%. The median duration of clinical benefit was 11 months with a time to progression of 6.5 months. The median duration of clinical benefit in our series is similar to that reported in two phase II trials with the sequence aminogluthetimide $\rightarrow$ formestane and aminogluthetimide $\rightarrow$ exemestane as third-line hormonal therapy, suggesting a non-cross-resistance between the two classes of inhibitors.

Keywords: Postmenopausal metastatic breast cancer (PMBC); Anastrozole; Formestane

1. Introduction

Anastrozole (ANZ), letrozole (LTZ), and exemestane (EXE) are effective first-line treatment for patients with endocrine responsive metastatic breast cancer [1]. Patients treated with a first-line aromatase inhibitor are likely to acquire drug-resistance and the most appropriate second-line endocrine therapy has not been established so far. Tamoxifen may be an effective second-line therapy in advanced breast cancer refractory to ANZ [2]. In a study by Harper-Wynne and Coombes [3], 9 out of 12 postmenopausal metastatic breast cancer (PMBC) women, previously showing a clinical benefit (CB) by formestane (FOR), achieved further stable disease (SD) by ANZ. It has been suggested that FOR markedly inhibits the aromatase activity even though pre-treatment with ANZ produces an increase of this activity [4].

2. Patients and methods

To explore the different sequence interactions between reversible non-steroidal (ANZ and LTZ) and non-reversible steroidal aromatase inhibitors (FOR and EXE), we evaluated the clinical benefit (CB = CR + PR + SD $\geq$ 6 months), according to the British Breast Group recommendations [5], in PMBC patients who had previously received ANZ 1 mg per day and subsequently, FOR 250 mg biweekly from 1996 to 2000. The patients received FOR if they showed PD after at least 12 weeks or more since they started receiving ANZ. The median age of the 21 patients identified at the time of FOR initiation was 64 years. Nineteen out of 21 patients received FOR after ANZ, with no other concomitant treatment. The remaining two patients received FOR and first-line chemotherapy after ANZ. Eighteen patients had previously received adjuvant therapy (6 on tamoxifen and chemotherapy, 10 only on tamoxifen, 2 only on chemotherapy) and 9 patients received first-line chemotherapy before ANZ.

* Corresponding author. Tel.: +39-06-52666919; fax: +39-06-52665637.
E-mail address: pcarlini@iol.it (P. Carlini).

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Table 1
Patient characteristics and site-related response to anastrozole and formestane (21 patients)

Age (years)	Hormonal receptor	Chemotherapy adjuvant/first-line	Tamoxifen adjuvant/first-line before ANZ	Anastrozole/second-line	Metastatic site	Formestane/ 3rd line
71	Er+Pgr+	Yes/yes	No/yes	SD 4 months	Lung	PR 12 months[a]
65	Er? Pgr?	No/yes	Yes/yes	SD 6 months	Lung	SD 6 months
79	Er+Pgr+	No/no	No/no	SD 10 months	Bone and lung	SD 4 months
60	Er+Pgr?	Yes/no	No/yes	SD 12 months	Soft tissue	PD 2 months
40	Er−Pgr−	Yes/no	Yes/no	SD 12 months	Bone	SD 3 months
50	Er+Pgr+	Yes/no	Yes/no	SD 12 months	Bone	SD 12 months
64	Er+Pgr+	No/no	No/yes	SD 14 months	Bone and lung	SD 7 months
56	Er?Pgr?	No/yes	No/yes	SD 14 months	Bone	SD 15 months
49	Er+Pgr+	Yes/yes	Yes/no	CR 15 months	Lung	SD 18 months
64	Er?Pgr?	No/no	Yes/yes	SD 17 months	Bone and soft tissue	SD 6.5 months
79	Er+Pgr+	Yes/no	Yes/no	SD 21 months	Bone	SD 6 months[a]
68	Er+Pgr+	No/no	Yes/no	SD 11 months	Bone	SD > 21 months
50	Er+Pgr+	Yes/no	Yes/no	SD 23 months	Lung	SD 3 months
62	Er+Pgr+	No/no	Yes/no	SD 5 months	Bone	SD 7 months
55	Er?Pgr?	No/yes	Yes/no	PR 18 months	Soft tissue, bone and lung	SD 11 months
60	Er+Pgr−	No/yes	Yes/no	SD 13 months	Soft tissue and bone	SD 3 months
48	Er+Pgr+	No/yes	Yes/no	SD 13 months	Lung and bone	SD 3 months
59	Er+Pgr+	Yes/no	Yes/no	SD 24 months	Bone	SD 21 months
72	Er+Pgr+	No/no	Yes/no	SD 12 months	Bone	SD 6 months
78	Er?Pgr?	No/yes	Yes/no	SD 12 months	Soft tissue	SD 6 months
73	Er?Pgr?	No/yes	Yes/no	SD 20 months	Bone	SD 4 months

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ?: unknown.
[a] After chemotherapy.

3. Results

In 19 out of 21 patients (90.5%), a CB response was achieved by ANZ, with a median duration of 12 months: 1/21 patients achieved a complete response, 1/21 patients showed a partial response, and 17/21 had stable disease $\geq$ 6 months, while in two patients we observed a SD $<$ 6 months. The higher CB obtained in the ANZ group might be related to the presence of bone as the only metastatic site in 43% of women and to the prior treatments received: adjuvant chemotherapy (38%), first-line chemotherapy (47.6%), combination of tamoxifen and chemotherapy (71%). Out of the 21 women progressing on ANZ, 12 achieved SD $\geq$ 6 months by FOR only. Out of the two patients who received chemotherapy after ANZ, one achieved a partial response and the other achieved SD $\geq$ 6 months. The overall CB was 66.5%—six patients obtained SD $<$ 6 months. The median duration of CB was 11 months with a time to progression of 6.5 months (Table 1).

4. Discussion

Tumors progressing on non-steroidal aromatase inhibitors may show a response to EXE [6], but the reverse scenario has also been described for tumors previously progressing on FOR [3]. The median duration of CB in our series is similar to that reported in two phase II trials with the sequence aminogluthetimide (AG) $\rightarrow$ FOR and AG $\rightarrow$ EXE as third-line hormonal therapy [7,8], suggesting a non-cross-resistance between the two classes of inhibitors.

The reversible inhibitors potentially increase aromatase activity in vitro, whereas irreversible inhibitors decrease this activity, theoretically justifying our sequence [9]. Letrozole is consistently 10–30 times more potent than anastrozole in inhibiting intracellular aromatase in human cancer cell lines [10]. ANZ provides a more consistent suppression of serum estradiol (E_2) levels compared with FOR [11], but LTZ is a more potent suppressor of plasma estrogen levels compared with ANZ [12]. In addition, tissue E_2 concentrations in transplanted tumors treated with ANZ and FOR are higher than those in tumors treated with LTZ, suggesting that tissue E_2 concentrations could reflect the amount of E_2 available in the tumor microenvironment [13]. Furthermore, the half-life of ANZ in rodents has been reported to be considerably shorter than that of LTZ [14], explaining why ANZ may not completely inhibit tumor aromatase activity and tumor growth. In the nude mouse model, Long et al. [13] suggests that tumors progressing on LTZ may not be sensitive to an additional steroidal or non-steroidal aromatase inhibitor, because of the potent ability of LTZ to inhibit aromatase. In this model, the complete suppression of estrogen and the long duration of response with LTZ in previously untreated tumors may lead to complete hormone independence. For all these reasons, it is possible that the lower potency of ANZ compared to LTZ in PMBC patients [12] may account for the subsequent response to FOR in our series. Further research is needed before drawing any firm conclusion.

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