

# Combination of Aromatase Inhibitors with Metronomic Capecitabine: A New Chemoendocrine Treatment for Advanced Breast Cancer

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## Abstract

**Purpose:** Endocrine therapy is one of the main treatment options for hormone receptor (HR)-positive advanced breast cancer (ABC). However, whether the combination of endocrine therapy with chemotherapy is practicable and more effective than endocrine therapy alone remains unknown. The aim of this study was to investigate the clinical efficacy of the aromatase inhibitors (AIs) combined with metronomic capecitabine to provide the clinical evidence for further research in patients with HR-positive ABC. **Methods:** Data from 407 patients with HR-positive ABC were retrospectively analyzed. A total of 305 patients were given AIs alone, and 102 patients were given AIs plus capecitabine as first-line treatment. Progression-free survival (PFS) was the primary endpoint. **Results:** The median follow-up for all patients was 47.0 months (range, 3 - 119 months). The median overall survival (OS) and PFS were 52.0 months and 24.2 months, respectively. The median PFS in the combination group was significantly longer than that in the AIs group (22.0 months vs. 14.0 months,  $p = 0.002$ ). Additionally, patients in the combination group had significantly longer OS than patients in the AI group (66.0 months vs. 49.0 months,  $p = 0.003$ ). Multivariate analysis showed that combination therapy was a significant favorable predictor for PFS and OS. Furthermore, young age (<40 years), low estrogen receptor (ER) expression level (<40%), presence of visceral metastasis, prior adjuvant AI use and long disease-free interval (DFI) (>24 months) improved the benefit from combination therapy. **Conclusions:** AIs plus metronomic capecitabine significantly improves PFS and OS in patients with HR-positive ABC. Thus, chemo-endocrine therapy

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should be further explored.

## Keywords

Advanced Breast Cancer, HR, Endocrine Resistance, Chemoendocrine Therapy, Survival

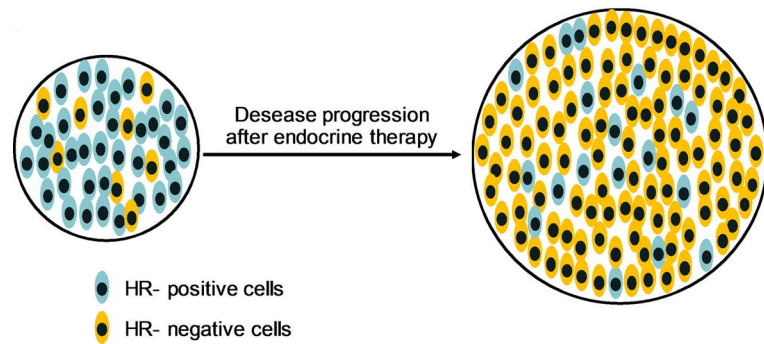
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## 1. Introduction

Breast cancer is the most common cause of cancer death in women [1]. Approximately 20% to 30% patients with early-stage breast cancer will eventually progress to metastatic disease [2], and 6% to 10% of newly diagnosed breast cancer cases are metastatic [3]. Except for cases with visceral metastasis, larger tumor burden and rapid growing tumors, guidelines recommend endocrine therapy as the preferred treatment option for hormone receptor (HR)-positive advanced breast cancer (ABC) [4] [5]. Although endocrine therapy has shown good efficacy and tolerance in both early- and advanced-stage disease, drug resistance is inevitable. Substantial efforts have been recently made to overcome resistance to endocrine therapy. New endocrine therapies, such as estrogen receptor (ER) degraders (fulvestrant), which directly bind to HRs, have been developed [6]. In addition, mTOR inhibitors and CDK4/6 inhibitors, which target the bypass pathways activated in the mechanisms of endocrine treatment resistance, have greatly improved progression-free survival (PFS) and overall survival (OS) in patient with ABC [7] [8]. Precision and targeted treatments are being developed against endocrine treatment resistance. However, some patients experiencing disease progression after endocrine therapy may actually have pseudo-resistance (Figure 1). In other words, these patients experience disease progression following endocrine therapy not because of resistance but because of the proliferation of HR-negative cells over time. Metronomic chemotherapy (MC) as a new regime of low-dose and continuous chemotherapy is efficient and well tolerated [9]. We thus speculate that metronomic chemotherapy combined with endocrine therapy to target different cells in HR-positive ABC may be more effective than endocrine therapy alone.

Decades ago, a number of studies had suggested that the combination of tamoxifen and chemotherapy not only reduced efficacy but also led to additional toxicity [10] [11] [12]. Therefore, at that time, a consensus was reached that endocrine therapy should not be used in combination with chemotherapy. However, with the development of new generations of endocrine treatments, the situation has been reversed. *In vitro* and *in vivo* experiments suggest that combination of aromatase inhibitors (AIs) or fulvestrant with chemotherapy exerts a synergistic effect on the suppression of tumor growth [13] [14] [15].

Recently, data from clinical trials demonstrated a therapeutic potential for the combination of AIs or fulvestrant with chemotherapy in HR-positive ABC and combination of therapy, especially capecitabine metronomic chemotherapy, was



**Figure 1.** HR-negative cells proliferate after endocrine therapy.

well tolerated and efficient [16] [17] [18]. Based on existing evidence, it is reasonable to assume that the combination of new-generation endocrine therapy and metronomic chemotherapy may be a good choice for HR-positive ABC.

The aim of this retrospective study was to evaluate the clinical efficacy of a synchronous therapy, metronomic chemotherapy with oral capecitabine in combination with third-generation AIs for HR-positive ABC to provide the clinical evidence for further research.

## 2. Patients and Methods

### 2.1. Study Population

The eligible patients were diagnosed with HR-positive and human epidermal growth factor receptor type 2 (HER2)-negative invasive breast cancer and treated at Sun Yat-sen University Cancer Center from January 2012 to December 2015. Patients were included based on the following criteria: 1) metastatic breast cancer; 2) histological confirmation of invasive breast cancer; 3) ER- and/or progesterone receptor (PR)-positive, HER2-negative advanced cancer; 4) availability of complete medical records and follow-up status; 5) no prior treatment after diagnosis of metastatic breast cancer. A total of 407 patients with ABC were recruited in this study. The study was reviewed and approved by the Institutional Review Board of Sun Yat-sen University Cancer Center.

### 2.2. Treatments and Evaluation

Of the 407 ABC patients, 305 were treated with AIs alone, and 102 were treated with AIs plus metronomic capecitabine as first-line treatment. AIs included letrozole, anastrozole or exemestane. The dosage was respectively 10 mg, 1 mg, and 25 mg once daily. Capecitabine was administered at 500 mg 3 times daily. In addition, all premenopausal patients were under ovarian suppression, including monthly hormone injections or surgery to remove the ovaries. Treatment continued until disease progression or the emergence of intolerable toxicity. The reduction of the capecitabine dose was permitted: an initial reduction to 500 mg twice daily and a subsequent reduction to 500 mg once daily if 2 degrees or above toxicity according to CTCAE 4.1. AIs were not applied with reduction of

doses. Response to treatment was evaluated by computed tomography or magnetic resonance imaging every 2 months until disease progression according to the response evaluation criteria in solid tumors [19].

### 2.3. Statistical Analyses

The primary endpoint of this study was PFS, defined as the time from the beginning of treatment for metastatic breast cancer to disease progression or death from any cause. The secondary endpoint was OS, defined as the period from the date of treatment for metastatic breast cancer to the date of death from any cause or the date of last follow-up. Clinicopathologic parameters were assessed between the two groups by chi-square test. The median PFS and OS were calculated by using the Kaplan-Meier method. Survival rates were compared by log-rank test. Multivariate analyses were performed using the Cox regression model for PFS and OS to identify independent factors and adjust for baseline characteristics. All analyses were performed using SPSS for Windows version 20.0 (IBM Corp. Armonk, USA). All statistical tests were two-sided, and  $p$  values  $< 0.05$  were considered significant.

The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (<http://www.researchdata.org.cn>), with the approval RDD number as RDDA2018000599.

## 3. Results

### 3.1. Patient Characteristics and Treatment

The clinicopathologic characteristics of the 407 patients in this study are described in **Table 1**. The median age was 45 years (range, 21 - 72 years) in the AI group and 44 years (range, 24 - 75 years) in the combination group. The number of patients with ER levels  $\leq 40\%$ ,  $40\% - 70\%$  and  $\geq 70\%$ , visceral metastasis or disease-free interval (DFI)  $> 24$  months was not significantly different between the two groups. A higher proportion of patients in the combination group used adjuvant AIs than that in the AI group (70.6% vs. 53.4%,  $p = 0.002$ ).

### 3.2. PFS and OS

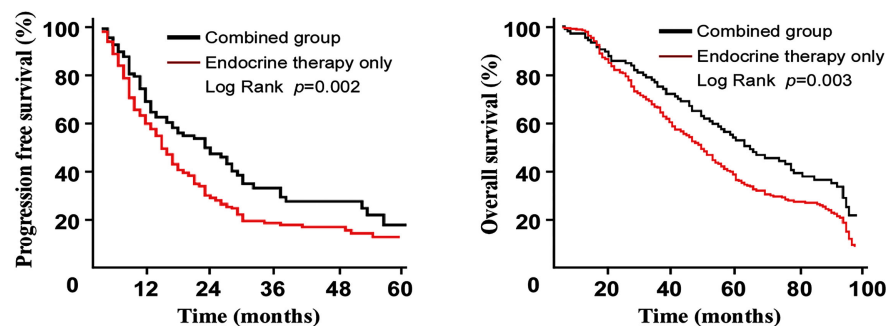
The median follow-up for all patients was 47.0 months (range, 3 - 119 months). During the follow-up period, a total of 305 patients died, including 236 (77.4%) patients in the AI group and 69 (22.6%) patients in the combination group. The 4-year PFS rates in the AI and combination groups were 10.8% and 23.2%, respectively. The 4-year OS rates in the AI and combination groups were 52.0% and 63.3%, respectively.

The median OS and PFS for all patients were 52.0 months and 14.0 months, respectively. The median PFS in the AI group was significantly shorter than that in the combination group (14.0 months vs. 22.0 months,  $p = 0.002$ ). Additionally, the median OS in the AI group was significantly shorter than that in the combination group (49.0 months vs. 66.0 months,  $p = 0.003$ ) (**Figure 2**).

**Table 1.** Clinical characteristics and treatment of breast cancer patients.

Characteristics	AIs group	Combination group	p value
	N (%)	N (%)	
Age (years)			
≤40	189 (62.0%)	61 (59.8%)	0.725
>40	116 (38.0%)	41 (40.2%)	
ER level			
≤40%	115 (50.2%)	50 (49.0%)	0.078
40% - 70%	111 (36.4%)	30 (29.4%)	
≥70%	41 (13.4%)	22 (21.6%)	
Visceral metastasis			
No	134 (43.9%)	43 (42.2%)	0.754
Yes	171 (56.1%)	59 (57.8%)	
Adjuvant AIs			
No	142 (46.6%)	30 (29.4%)	0.002*
Yes	163 (53.4%)	72 (70.6%)	
Disease-free interval			
≤24 months	173 (64.4%)	53 (52.0%)	0.402
>24 months metastasis	132 (35.6%)	49 (48.0%)	
Liver	57 (18.7%)	16 (15.7%)	0.514
Lung	65 (21.2%)	35 (34.3%)	
Bone	187 (61.3%)	65 (63.7%)	
Local recurrence	89 (29.2%)	38 (37.2%)	

ER: estrogen receptor; AIs: aromatase inhibitors. Statistical analysis was performed using  $\chi^2$  test. Statistically significant differences are labeled \*.

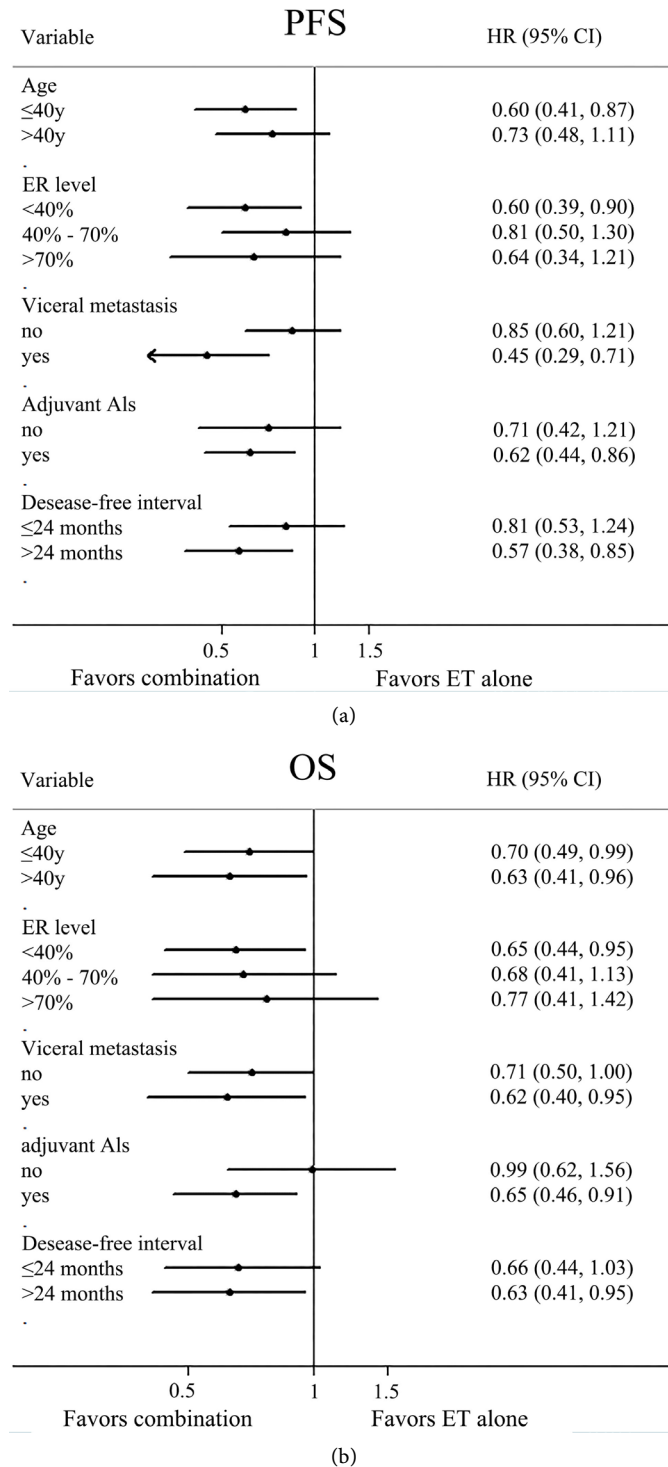


**Figure 2.** The PFS and OS in the combination group were significantly longer than that in the endocrine therapy group.

### 3.3. Effects of Prognostic Factors on PFS and OS

To evaluate the independent role of various variables in PFS and OS, we performed a multivariate analysis including age, ER level, visceral metastasis, adjuvant AI use, DFI and combination therapy. The presence of visceral metastasis was an adverse prognostic factor for PFS and OS. The combination of AIs with capecitabine was a favorable prognostic factor for PFS and OS. Moreover, lower ER expression level (<40%), presence of visceral metastasis, relapse following adjuvant AIs and shorter DFI were adverse prognostic factors for OS but not for PFS (Table 2).

To explore the benefit from combination therapy, we performed univariate analysis, which showed that lower ER expression level (<40%), presence of visceral metastasis, prior adjuvant AI use and longer DFI (>24 months) significantly improved the benefit from combination therapy (Figure 3).



**Figure 3.** Lower ER expression level ,visceral metastasis, prior adjuvant AI use and longer DFI improved the benefit from combination therapy.

**Table 2.** Multivariate analysis of PFS and OS in all population.

Variables	PFS			OS		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age, years ( $\leq 40$ vs. $>40$ )	0.94	0.74 - 1.20	0.627	1.01	0.79 - 1.28	0.960
ER level ( $<40\%$ vs. $\geq 40\%$ )	0.98	0.74 - 1.30	0.895	0.43	0.32 - 0.59	$<0.001^*$
Visceral metastasis (no vs. yes)	1.29	1.02 - 1.63	0.035*	1.54	1.22 - 1.95	$<0.001^*$
Adjuvant AIs (no vs. yes)	0.91	0.67 - 1.23	0.540	2.71	2.00 - 3.67	$<0.001^*$
DFI ( $\leq 24$ months vs. $>24$ months)	0.97	0.75 - 1.24	0.781	0.34	0.27 - 0.44	$<0.001^*$
AIs plus Cap. (no vs. yes)	0.65	0.49 - 0.87	0.003*	0.72	0.55 - 0.95	0.020*

ER: estrogen receptor; AIs: aromatase inhibitors; Cap: capecitabine; HR: hazard ratio; HR and 95% CIs were calculated using COX regression analysis. Statistically significant differences are labeled \*. DFI: disease-free interval.

#### 4. Discussion

Endocrine therapy is generally the first treatment option for HR-positive ABC. The PFS of patients treated with first-line tamoxifen, AIs and fulvestrant is approximately 6 months, 9 - 13 months and 17 - 23 months, respectively [20] [21] [22] [23] [24]. In other words, all patients inevitably experience disease progression. Various mechanisms, either intrinsic or acquired, could be implicated in endocrine therapy resistance [25]. However, in some patients, disease progression following endocrine therapy may not be because of endocrine resistance but rather due to the proliferation of some HR-negative cancer cells during the period of endocrine therapy. In some cases, ten percent of cells can be HR-negative, even though 90% of cells are HR-positive. Therefore, endocrine therapy alone is not sufficient to suppress the growth of so called “HR-positive” breast cancer. Additionally, in this study, we are interested in the theoretical basis of chemo-endocrine therapy.

The results of some preclinical studies on the efficacy of chemo-endocrine therapy are still uncertain [10] [14] [15] [26] [27] [28] [29]. In the past, it had been proposed that tamoxifen induced the accumulation of breast cancer cells in the G0/G1 phase and that cells in this phase of the cell cycle were not sensitive to chemotherapy (epirubicin plus cyclophosphamide) [10]. The combined use of chemotherapy and tamoxifen in early-stage breast cancer is not realistic [11] [30] and is not recommended by guidelines. However, AIs and fulvestrant are currently widely used for HR-positive breast cancer. They have different mechanisms of action and superior efficacy in comparison with tamoxifen. Several clinical trials also show that AIs or fulvestrant plus intravenous or oral chemotherapies result in high overall response rate or prolonged PFS in patients with HR-positive ABC [16] [18] [31]. These results show that the combination of endocrine therapy with metronomic chemotherapy may be a rational option without any antagonistic effect.

Our results suggested that compared with AIs alone, AIs plus metronomic capecitabine as first-line therapy significantly improved PFS and OS in patients

with ABC. In particular, patients with low ER expression, visceral metastasis, prior adjuvant AI therapy and prolonged DFI displayed obvious benefits from chemo-endocrine therapy. Patients with lower ER expression level had a lower response to endocrine therapy [32]. The presence of visceral metastasis and short DFI suggests an unfavorable prognosis [33]. Response to AIs following adjuvant AIs may be significantly lower than that to treatments without prior adjuvant AIs [22] [34]. In brief, patients with HR-positive ABC with unfavorable prognostic factors or patients who are insensitive to endocrine therapy may be candidates for chemo-endocrine therapy.

Nevertheless, we recognize there are several limitations to this study. First, this study was a retrospective analysis. Second, selective bias might be inevitable (e.g., the combination group had a higher proportion of patients who received adjuvant AIs than the AI group, and the reason might be that clinicians were more likely to use combination therapy if patients had already received adjuvant AIs). Despite these limitations, our results demonstrate that the combination of AIs with metronomic capecitabine significantly improves PFS and OS in patients with HR-positive ABC. Chemo-endocrine therapy may thus be considered a therapeutic strategy for these patients. We are currently conducting a larger randomized controlled phase 3 trial to support our findings (NCT02767661).

### Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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