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Advanced breast cancer updates on anastrozole versus tamoxifen☆

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Abstract

Results from two studies, the North American trial and the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability (TARGET) trial carried out in Europe/rest of the world comparing 'Arimidex' (anastrozole) 1 mg with tamoxifen 20 mg for treatment of advanced breast cancer in postmenopausal women, have previously been reported individually and as a prospectively combined analysis. For the combined analysis, at a median follow-up of 18.2 months anastrozole was shown to be superior to tamoxifen in terms of time to progression (TTP; $P = 0.022$) in the hormone receptor-positive subgroup. Both treatments were well tolerated; anastrozole was associated with significantly fewer thromboembolic events ($P = 0.043$) and fewer reports of vaginal bleeding. The survival analyses and safety update in the overall population and in the hormone receptor-positive subgroup from the combined data are now available. At a median follow-up of 43 months, 56.0% of patients in the anastrozole group and 56.1% of patients in the tamoxifen group had died. At the cut-off date, 2-year mortality rates were 31.7 and 32.5% with anastrozole and tamoxifen, respectively, in the overall population. Median time to death (TTD) was similar for both treatments (39 months versus 40 months, respectively; hazard ratio (HR) 0.97, lower 95% confidence limit (CL) 0.84). Similar findings were reported in the hormone receptor-positive population. With longer follow-up, both anastrozole and tamoxifen remained well tolerated. Sequencing data showed that patients crossed from anastrozole to tamoxifen or tamoxifen to anastrozole are similar regarding efficacy. In conclusion, these TTP, survival and tolerability data support the use of anastrozole as a first-line therapy of choice in postmenopausal women with advanced breast cancer.

Keywords: Endocrine therapy; Arimidex; Tamoxifen; Aromatase inhibitor; Advanced breast cancer; Time to progression; Estrogen receptor

1. Introduction

Endocrine therapy, primarily directed at reducing the synthesis of estrogen, or alternatively blocking estrogen receptors in hormone-sensitive tumors, is a widely accepted treatment modality for breast cancer. For the past 25 years the estrogen receptor antagonist tamoxifen has been successfully used to treat women with early and advanced breast cancer. Despite its proven efficacy, tamoxifen is associated with certain side effects and resistance to treatment [1]. Alternative therapies, which show a lack of cross resistance across classes of endocrine therapies have therefore been developed, including the aromatase inhibitors (AIs), which block the conversion of androgens to estrogen, reducing estrogen synthesis; they are used in patients with postmenopausal status (natural, surgical or pharmacological).

Anastrozole, an oral, third-generation, non-steroidal aromatase inhibitor [2], is well tolerated, and both potent and selective, providing near maximal estrogen suppression in both the peripheral circulation and within the tumor itself [3,4]. It was the first aromatase inhibitor to show a significant survival advantage over megestrol acetate in the second-line advanced breast cancer setting [2]. It has been suggested that potent estrogen suppression via aromatase inhibition may result in greater tumor response than with tamoxifen, particularly as tamoxifen is also known to be a weak or partial estrogen agonist in addition to being an estrogen antagonist [5].

To investigate the suitability of anastrozole as first-line treatment for advanced breast cancer in postmenopausal women, anastrozole and tamoxifen were compared in two similar randomized trials. One trial was conducted in the United States (US) and Canada (the North American trial) [6] and the other was conducted in Europe, Australia, New Zealand, South America and South Africa (Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability (TARGET) trial) [7]. Both trials were similar in design to allow for both an individual and a prospectively planned combined analysis. The findings of these individual trials

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and the combined analysis are summarized here and have been published in detail previously [6–8]. In addition, the results of the survival analyses and safety update in the overall population and the hormone receptor-positive subgroup from the combined data are reported in this article. Finally, it was important to investigate whether or not the change in sequence of administration from tamoxifen followed by anastrozole to anastrozole followed by tamoxifen would impact on the overall benefit to patients provided by the two drugs. To determine if tamoxifen was effective as a second-line therapy in patients progressing on anastrozole treatment (and vice versa), a retrospective collection of data from the North American and TARGET first-line trials was carried out. The results of this analysis are also presented here.

2. Methodology

Both trials were randomized, double-blind and multicentered, and designed to compare the efficacy and tolerability of anastrozole 1 mg once daily (od) with tamoxifen 20 mg od as first-line therapy for advanced breast cancer in postmenopausal women. Patients were either newly diagnosed with advanced breast disease or had progressed following diagnosis and treatment of early disease and were suitable for endocrine therapy as first-line treatment. Patients were required to have estrogen receptor-positive and/or progesterone receptor-positive (hormone receptor-positive) tumors or have unknown status. Prior adjuvant chemotherapy for early breast cancer was permissible; however, patients were not allowed to have had any prior chemotherapy for advanced disease, and patients must not have received adjuvant tamoxifen within 12 months prior to entry into the trial. Primary endpoints were TTP, objective response and tolerability. Trial treatment was continued until objective disease progression was observed, and follow-up was performed until death. Participants in both trials had comparable baseline demographics. Detailed methodology for these trials is available elsewhere [6–8].

3. Results

3.1. North American trial

In total, 353 patients at 97 sites in the US and Canada were randomized to treatment on a 1:1 basis (anastrozole 1 mg, $n = 171$; tamoxifen 20 mg, $n = 182$). At the time of analysis, the median duration of follow-up was 17.7 months. Baseline patient demographic characteristics were well balanced [6].

3.1.1. Efficacy

The efficacy results are summarized in Table 1. In brief, anastrozole was superior to tamoxifen in terms of TTP (median TTP: 11.1 months for the anastrozole group compared with 5.6 months for the tamoxifen group) with a HR of 1.44 (lower one-sided 95% CL 1.16; $P = 0.005$). Disease progression was the main reason for treatment failure in both treatment groups (67.8% of patients in the anastrozole group and 75.3% of patients in the tamoxifen group) [6].

3.2. TARGET trial

In total, 668 patients from 83 sites in Europe, Australia, New Zealand, South America and South Africa were randomized to treatment on a 1:1 basis (anastrozole 1 mg, $n = 340$; tamoxifen 20 mg, $n = 328$). At the time of the major analysis, the median duration of follow-up was 19 months. Baseline patient demographic characteristics were well balanced [7].

3.2.1. Efficacy

The efficacy results are summarized in Table 1. Anastrozole was at least as effective as tamoxifen in terms of TTP (median TTP: 8.2 months for the anastrozole group compared with 8.3 months for the tamoxifen group) with a HR of 0.99 (lower one-sided 95% CL 0.86; $P = 0.941$) [7].

Table 1
North American and TARGET trials efficacy results

	North American trial			TARGET trial		
	Anastrozole 1 mg ($n = 171$)	Tamoxifen 20 mg ($n = 182$)	Hazard ratio (lower 95% CL)	Anastrozole 1 mg ($n = 340$)	Tamoxifen 20 mg ($n = 328$)	Hazard ratio (lower 95% CL)
Disease progression (%)	67.8	75.3		69.4	69.2	
Median TTP (months)	11.1	5.6	1.44 (1.16[c])	8.2	8.3	0.99 (0.86[b])
Best objective response (CR + PR, %)	21.0	17.0		32.9	32.6	
Clinical benefit[a] (%)	59.1[d]	45.6		56.2	55.5	

CL, confidence limit; TTP, time to progression; CR, complete response; PR, partial response; SD, stable disease.
[a] CR + PR + SD ≥ 24 weeks.
[b] $P = 0.941$ (two-sided).
[c] $P = 0.005$ (two-sided).
[d] $P = 0.0098$ (two-sided, retrospective analysis).

3.3. Combined analysis

The combined population was 1021 patients (anastrozole 1 mg, $n = 511$; tamoxifen 20 mg, $n = 510$). The median duration of follow-up was 18.2 months. Although patient demographics and pretreatment characteristics were generally similar between the two trials, there was a major difference in the proportion of patients with confirmed hormone receptor-positive tumors. In the TARGET trial, only 300/668 patients (45%) had known hormone receptor-positive status, whereas 314/353 of patients (89%) in the North American trial were known to have hormone receptor-positive tumors. This resulted in 614/1021 patients (60%) with known hormone receptor-positive status in the combined population [8].

3.3.1. Efficacy

Analysis of the TTP data showed there was no statistically significant difference between the treatment groups (8.5 months versus 7.0 months for anastrozole and tamoxifen, respectively). The Kaplan–Meier curve for the overall population is shown in Fig. 1. The estimated progression HR for tamoxifen versus anastrozole was 1.13 (lower 95% CL 1.00; $P = 0.103$); this confirms the findings of the individual studies that anastrozole is at least as effective as tamoxifen [8].

3.3.2. Subanalysis of patients with known hormone receptor-positive tumors

Efficacy of anastrozole relative to tamoxifen was explored within subgroups defined retrospectively by hormone receptor status. In the subanalysis of patients with known hormone receptor-positive tumors, TTP was significantly longer with anastrozole compared with tamoxifen ($P = 0.022$); median TTP was 10.7 months for the anastrozole group and 6.4 months for the tamoxifen group. The Kaplan–Meier curve for patients with known hormone receptor-positive tumors is shown in Fig. 2 [8].

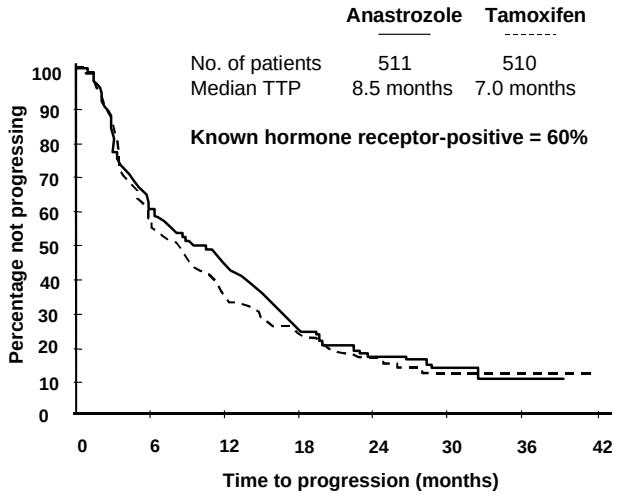

Fig. 1. Kaplan–Meier probability of time to progression in the overall population for the combined analysis of the North American and TARGET trials.

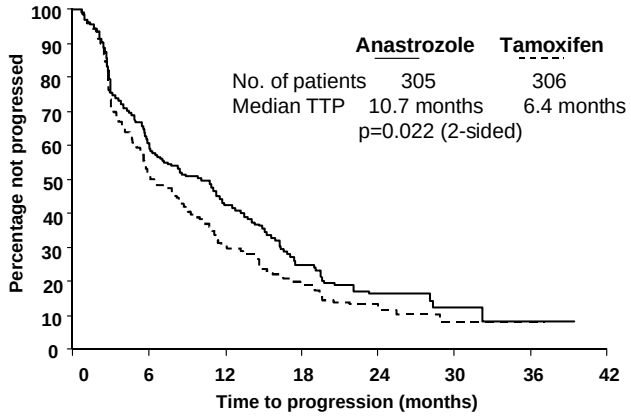

Fig. 2. Kaplan–Meier probability of time to progression for patients with known hormone receptor-positive tumors for the combined analysis of the North American and TARGET trials.

3.3.3. Tolerability

In line with both the individual trials [6,7], the combined analysis at median follow-up of 18.2 months showed that anastrozole and tamoxifen were both well tolerated in the majority of patients. The incidence of pre-defined adverse events reflected the findings of the two individual trials (Table 2) [8]. Anastrozole was associated with fewer incidences of thromboembolic events (3.6% versus 6.5%, respectively) and vaginal bleeding (1.0% versus 2.2%, respectively) compared with tamoxifen.

3.3.4. Updated tolerability

With longer follow-up (median follow-up 43 months), both anastrozole and tamoxifen remained well tolerated; anastrozole continued to be associated with fewer reports of thromboembolic events (5.3% versus 9.0%, respectively) and vaginal bleeding (1.0% versus 2.5%, respectively) compared with tamoxifen [9].

Table 2
Tolerability data from combined analysis of the North American and TARGET trials at median follow-up of 18.2 months

	Anastrozole, *n* (%)	Tamoxifen, *n* (%)
Depression	23 (4.5)	32 (6.3)
Tumor flare	15 (3.0)	18 (3.5)
Thromboembolic disease	18 (3.6)	33 (6.5)
Gastrointestinal disturbance	170 (33.6)	196 (38.4)
Hot flashes	134 (26.5)	118 (23.1)
Vaginal dryness	9 (1.8)	3 (0.6)
Lethargy	6 (1.2)	15 (2.9)
Vaginal bleeding	5 (1.0)	11 (2.2)
Weight gain	11 (2.2)	8 (1.6)

Table 3
Patients alive at 24 months of treatment and median time to death at median follow-up of 43 months

	Anastrozole	Tamoxifen	Hazard ratio (lower 95% CL)
Overall population	$n = 511$	$n = 510$	0.97 (0.84)
24-month mortality; *n* (%) dead	159 (31.7)	163 (32.5)	
Median TTD (months)	39.0	40.0	
HR + population	$n = 305$	$n = 306$	1.00 (0.83)
24-month mortality; *n* (%) dead	97 (31.8)	95 (31.5)	
Median TTD (months)	41.0	41.5	

CL, confidence limit; HR+, hormone receptor-positive.

3.3.5. Survival

Analysis of the combined data from the two trials showed that anastrozole is as effective as tamoxifen with respect to 24-month mortality and median TTD in both the overall population and in the subgroup of patients with known hormone receptor-positive tumors (Table 3) [9].

3.4. Sequencing of treatments

Data from a questionnaire on the status of patients' tumors, documented by their clinicians, were collected retrospectively from the North American and TARGET trials. Additional subgroup analysis was carried out to determine whether the presence or absence of visceral metastases or hormone receptor-positive status at baseline had an impact on CB and OR. The clinical outcome was similar for all patients who crossed from anastrozole to tamoxifen or tamoxifen to anastrozole, including those who had intervening chemotherapy, hormonal therapy or combination of other hormonal therapy and chemotherapy (Table 4) [10]. Results for patients in all subgroups were similar to those for all patients (Table 4) [10].

Table 4
Sequencing data for all patients who crossed from anastrozole to tamoxifen or tamoxifen to anastrozole and in the subgroups of patients with or without hormone receptor-positive tumors and with or without visceral metastases

	Anastrozole → tamoxifen		Tamoxifen → anastrozole	
Overall population				
N	137		134	
OR, *n* (%)	12 (9)		7 (5)	
CB, *n* (%)	58 (42)		54 (40)	
HR status	+	Unknown/–	+	Unknown/–
n	84	53	95	39
OR, *n* (%)	6 (7)	6 (11)	3 (3)	4 (10)
CB, *n* (%)	35 (32)	23 (43)	39 (41)	15 (39)
Visceral metastases	Yes	No	Yes	No
n	52	85	59	75
OR, *n* (%)	6 (12)	6 (7)	3 (5)	4 (5)
CB, *n* (%)	22 (42)	36 (42)	21 (36)	33 (44)

Objective response (OR) = complete + partial response; clinical benefit (CB) = complete+partial response+stable disease ≥ 24 weeks; hormone receptor (HR).

4. Discussion

The data from the individual anastrozole/tamoxifen equivalence trials and the combined analysis involving over 1000 patients have demonstrated that anastrozole is at least as effective as tamoxifen for the first-line treatment of advanced breast cancer in postmenopausal women. The results from the North American trial demonstrated a significant improvement in median TTP and CB with anastrozole compared with tamoxifen ($P = 0.005$ and 0.0098, respectively). This was the first observation of a single endocrine agent showing significantly better efficacy than tamoxifen in first-line hormone therapy of postmenopausal patients with breast cancer.

The reasons for the apparent discrepancies in efficacy between the two trials were investigated. The most likely reason lies in the proportion of patients with tumors known to be hormone receptor-positive, which differed markedly between the North American trial (approximately 90% of patients) and the TARGET trial (approximately 45% of patients). Using the combined data set, an exploratory analysis of subgroups of patients defined by tumor receptor status (known hormone receptor-positive tumors versus tumors of unknown receptor status) indicated that anastrozole was significantly more beneficial compared with tamoxifen in terms of prolonging TTP ($P = 0.022$). This finding confirms that positive hormonal receptor status is a fundamental factor when investigating the comparative efficacy of two hormone therapies, in this case anastrozole and tamoxifen.

Both anastrozole and tamoxifen were well tolerated at the main analysis, and remained well tolerated with longer follow-up. The lower risk of thromboembolic events seen with anastrozole versus tamoxifen is particularly noteworthy in both studies.

Additionally, overall survival data show equal efficacy between anastrozole and tamoxifen. Furthermore, the retrospective analysis from the North American and TARGET trials indicates that tamoxifen is effective as a second-line therapy following anastrozole in the overall population. This is also true in subgroups of patients with or without hormone receptor-positive tumors or with or without visceral metastases. This observation is important, confirming that anastrozole does not induce any resistance to tamoxifen, and therefore justifies the use of tamoxifen after failure of anastrozole.

In conclusion, these data confirm that anastrozole has a favorable therapeutic index compared to tamoxifen and thus support the use of anastrozole as a first-line hormone therapy of choice for postmenopausal women with advanced breast cancer.

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