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'Arimidex' (anastrozole) versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer-efficacy overview☆

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Abstract

ATAC, a randomized, double-blind trial, compared tamoxifen (20 mg) with anastrozole ('Arimidex') (1 mg) alone, and the combination of anastrozole plus tamoxifen (combination), as adjuvant endocrine treatment for postmenopausal patients with early breast cancer. Patients with operable invasive breast cancer following completion of primary therapy, who were candidates to receive adjuvant endocrine therapy, were eligible for this study. Primary endpoints were disease-free survival (DFS) and tolerability. Other endpoints included time to recurrence (TTR: censoring non-breast cancer deaths before recurrence) and the incidence of contralateral breast cancer. A total of 9366 patients were included in this study ($N = 3125$, 3116 and 3125 for anastrozole, tamoxifen and the combination, respectively). Median duration of therapy was 30.7 months and median follow-up was 33.3 months. The total numbers of events were 317, 379 and 383 for anastrozole, tamoxifen and the combination, respectively. DFS was significantly improved in the overall population for anastrozole versus tamoxifen (hazard ratio (HR) = 0.81, 95% confidence interval (CI) (0.71–0.96), $P = 0.013$). Anastrozole showed improved TTR compared with tamoxifen (HR = 0.79, CI (0.67–0.94), $P = 0.008$), which improved even further in the ER+ and/or PR+ subgroup (HR = 0.73, CI (0.59–0.90), $P = 0.003$). The incidences of hot flushes, thromboembolic events, ischaemic cerebrovascular events, vaginal bleeding/discharge and endometrial cancer were significantly reduced with anastrozole compared with tamoxifen ($P < 0.03$ for all). Musculoskeletal disorders and fractures were significantly reduced in patients receiving tamoxifen compared with those on anastrozole ($P < 0.03$ for both). No increase in hip fractures was seen for anastrozole versus tamoxifen (11 versus 13, respectively). Combination treatment was equivalent to tamoxifen in terms of both efficacy and tolerability. Anastrozole showed superior efficacy to tamoxifen for DFS, TTR and contralateral breast cancer. Early findings show anastrozole to be an effective and well-tolerated endocrine option for the treatment of postmenopausal patients with early breast cancer. For the first time a choice now exists for adjuvant endocrine treatment for postmenopausal women with hormone responsive tumours. Longer follow-up will further define the benefit/risk of anastrozole adjuvant therapy.

Keywords: Anastrozole; Tamoxifen; Aromatase inhibitor; Early breast cancer; Postmenopausal women; ATAC; Randomized clinical trial; Adjuvant

1. Introduction

It is now recognized that anastrozole ('Arimidex') is effective and well tolerated in the treatment of advanced breast cancer. Anastrozole was originally approved for the second-line treatment of postmenopausal women who had failed on tamoxifen treatment, following data demonstrating a survival advantage and significantly less weight-gain compared with megestrol acetate [1–3]. Since 2000, anastrozole has also become available for first-line treatment, following data showing anastrozole to be superior to tamoxifen in terms of improved time to disease progression (TTP) and significantly fewer thromboembolic events in patients with advanced hormone-sensitive breast cancer [4].

In 2001, anastrozole became the first third-generation aromatase inhibitor to report in the treatment of early disease with the first analysis of the ATAC ('Arimidex', Tamoxifen Alone or in Combination) trial [5]. This report gives a brief overview of the efficacy and tolerability data from the ATAC trial and provides brief details on other ongoing adjuvant trials involving other aromatase inhibitors.

2. Trial design

ATAC was a randomized, double-blind trial that compared tamoxifen (20 mg) with anastrozole ('Arimidex') (1 mg)

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alone, and the combination of anastrozole plus tamoxifen, as adjuvant endocrine treatment for postmenopausal patients with early breast cancer [5]. Full details of the methodology are published elsewhere [5]. Patients with operable invasive breast cancer following completion of primary therapy were eligible for this study if they were also candidates to receive hormonal adjuvant therapy. The primary endpoints were disease-free survival (DFS) and tolerability. Other endpoints included time to recurrence (TTR: censoring non-breast cancer deaths before recurrence) and the incidence of contralateral breast cancer.

3. Results

3.1. Patients

A total of 9366 patients entered the trial (anastrozole: $N = 3125$; tamoxifen: $N = 3116$; combination: $N = 3125$). They were recruited from 381 centres in 21 countries between July 1996 and March 2000. The baseline characteristics, tumour and primary treatment options were well balanced across the treatment groups [5]. A total of 84% of patients were known to be oestrogen receptor-positive (ER+) and/or progesterone receptor-positive (PR+).

3.2. Efficacy endpoints

The major analysis was planned when there were 1056 events. A total of 1079 first events were recorded at the follow-up cut-off date 29 June 2001 (Table 1), with 766 of them being in women with hormone receptor-positive tumours. At this time the median duration of therapy was 30.7 months and the median follow-up was 33.3 months.

DFS was significantly improved in the overall population for anastrozole versus tamoxifen ($HR = 0.81$, 95% CI (0.71–0.96), $P = 0.013$) (Fig. 1). Anastrozole showed improved TTR compared with tamoxifen ($HR = 0.79$, 95% CI (0.67–0.94), $P = 0.008$), which improved even further in the ER+ and/or PR+ subgroup ($HR = 0.73$, 95% CI (0.59–0.90), P=0.003) (Fig. 2). Anastrozole was found to be superior to the combination arm with respect to both DFS and TTR in the overall population ($P = 0.06$ and 0.07, respectively) and the hormone receptor-positive population ($P = 0.002$ and 0.0001, respectively). Combination treatment was shown to be equivalent to tamoxifen in terms of DFS and TTR.

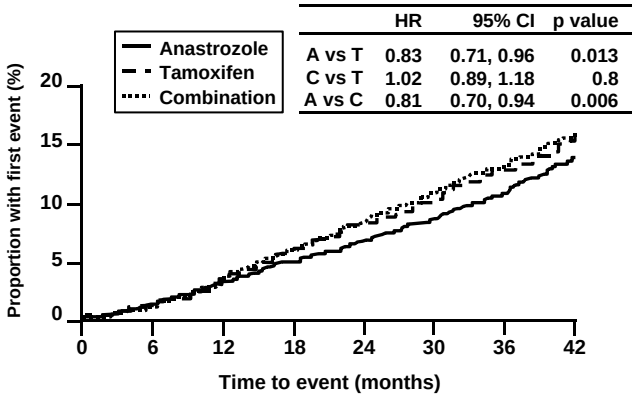

Fig. 1. Disease-free survival in the intention-to-treat population (reproduced with permission from Lancet 359 (9324) (2002) 2131–2139). A: anastrozole; T: tamoxifen; C: combination; HR: hazard ratio; CI: confidence interval.

The incidence of a new (contralateral) breast cancer as a first event was strikingly reduced in the anastrozole group (Fig. 3); when compared with tamoxifen the odds were reduced by 58% (Odds ratio = 0.42, 95% CI 0.22–0.79, $P = 0.007$).

An initial exploratory subgroup analysis suggested a potential interaction between anastrozole and tamoxifen for prior chemotherapy use compared with no previous chemotherapy. Possible explanations for this observation, including chance or differences in types of chemotherapy,

Table 1
Distribution of first events

	Anastrozole ($N = 3125$)	Tamoxifen ($N = 3116$)	Combination ($N = 3125$)	In total ($N = 9366$)
First events				
Local recurrence	67	83	81	231
Distant recurrence[a]	158	182	204	544
Contralateral breast cancer	14	33	28	75
Invasive	9	30	23	62
Ductal carcinoma in situ	5	3	5	13
Deaths before recurrence	78	81	70	229
Total	317 (10.1%)	379 (12.2%)	383 (12.3%)	1079 (11.5%)
Events at any time				
Distant recurrence[a]	180	203	232	615
Deaths after recurrence	122	122	145	389
All deaths	200	203	215	618

[a] Including five deaths (2, 1, 2, deaths on anastrozole, tamoxifen, and the combination, respectively), which were attributed to breast cancer without prior information about recurrence.

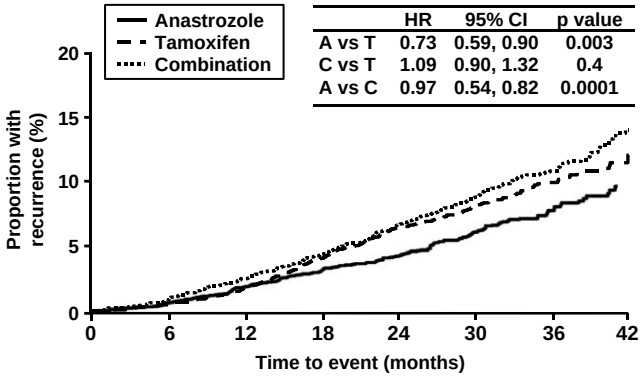

Fig. 2. Probability of recurrence in patients with hormone receptor-positive tumours (reproduced with permission from Lancet 359 (9324) (2002) 2131–2139). (Recurrence events including new contralateral tumours, censoring non-breast cancer causes before recurrence; A: anastrozole; T: tamoxifen; C: combination; HR: hazard ratio; CI: confidence interval.)

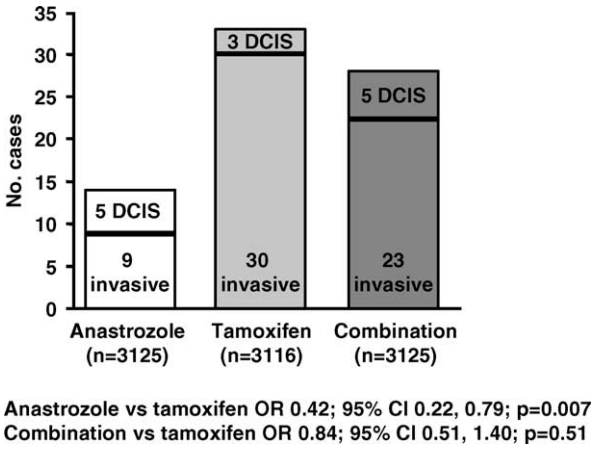

Fig. 3. The incidence of new (contralateral) breast cancers in the intention-to-treat population. DCIS: ductal carcinoma in situ; OR: odds ratio; CI: confidence interval.

are being investigated. Longer follow-up is required before any meaningful conclusions can be made.

3.3. Tolerability endpoints

The incidences of hot flushes ($P < 0.0001$), thromboembolic events ($P = 0.0006$), ischaemic cerebrovascular events ($P = 0.0006$), vaginal bleeding ($P < 0.0001$), vaginal discharge ($P < 0.0001$) and endometrial cancer ($P = 0.02$) were significantly reduced with anastrozole compared with tamoxifen (Table 2). Musculoskeletal disorders and fractures were significantly reduced in patients receiving tamoxifen compared with those on anastrozole ($P < 0.0001$ for both). No increase in hip fractures was seen for anastrozole versus

Table 2
Incidence of pre-specified adverse events in each treatment group

Adverse event	Anastrozole ($N = 3092$)		Tamoxifen ($N = 3094$)		Combination ($N = 3097$)		P values[a] A vs. T
	n	(%)	n	(%)	n	(%)	
Hot flushes	1060	34.3	1229	39.7	1243	40.1	<0.0001
Nausea and vomiting	324	10.5	315	10.2	363	11.7	0.7
Fatigue/tiredness	483	15.6	466	15.1	435	14.0	0.5
Mood disturbances	480	15.5	469	15.2	482	15.6	0.7
Musculoskeletal disorders	860	27.8	660	21.3	685	22.1	<0.0001[b]
Vaginal bleeding	138	4.5	253	8.2	238	7.7	<0.0001
Vaginal discharge	86	2.8	354	11.4	357	11.5	<0.0001
Endometrial cancer[c]	3	0.1	13	0.5	6	0.3	0.02
Fractures	183	5.9	115	3.7	142	4.6	<0.0001[b]
Hip[d]	11	0.4	13	0.4	10	0.3	–
Spine	23	0.7	10	0.3	14	0.5	–
Wrist/colles	36	1.2	25	0.8	27	0.9	–
Ischaemic cardiovascular disease	76	2.5	59	1.9	68	2.2	0.14
Ischaemic cerebrovascular event	31	1.0	65	2.1	51	1.6	0.0006
Venous thromboembolic events[e]	64	2.1	109	3.5	124	4.0	0.0006
Deep venous thromboembolic events including PE	32	1.0	54	1.7	63	2.0	0.02
Cataracts	107	3.5	116	3.7	105	3.4	0.6

[a] For all pre-defined adverse events, the differences observed between tamoxifen and the combination arm were not significant.
[b] In favour of tamoxifen.
[c] Excluding patients with hysterectomy at baseline, so that the total number of patients used as denominator was 2228, 2237, and 2240 for anastrozole, tamoxifen and the combination arms, respectively. For endometrial cancer, unlike other listed adverse events (which were based on those reported whilst on trial treatment), this is reported based on those events reported prior to disease recurrence. There were three cases of endometrial cancer (1 anastrozole, 2 tamoxifen) reported after stopping treatment, but pre-recurrence. It is not known whether there were any intervening therapies in the time after stopping initial treatment and prior to recurrence.
[d] For different fracture sites actual numbers reported. A: anastrozole; T: tamoxifen; PE: pulmonary emboli.
[e] Including deep venous thromboembolic events.

tamoxifen (11 versus 13, respectively). There was no difference in the incidence of pre-defined adverse events between the tamoxifen and the combination groups (Table 2).

4. Is it time to change clinical practice?

Following the first presentation of the ATAC trial data in December 2001 at the San Antonio Breast Cancer Symposium, there has been much discussion within the medical community about how and when the results from this trial should be implemented into clinical practice.

Concerns have been raised about immaturity of the data from the ATAC trial. It is known that a 5-year course of tamoxifen is required to see the full benefits of treatment [6], while the first analysis of the ATAC data was performed at a median duration of <3 years of follow-up, with median duration of therapy 30.7 months, and no 5-year data. Previous adjuvant hormonal trials conducted in patients with early breast cancer have shown that a difference in efficacy observed at a 'relatively early' stage was maintained over time [7–9]. The majority of patients in the ATAC trial had received 2–3 years (43%) or 3–4 years (30%) of treatment. At this analysis, however, anastrozole produced a 17% relative risk reduction in DFS in the overall population and a 27% relative risk reduction in TTR in the hormone receptor-positive population, when compared with tamoxifen. Since TTR is such a robust surrogate for long-term survival, it is expected that the efficacy benefit with anastrozole will persist, with further follow-up providing additional information on distant recurrence rates and survival.

It could be argued that the full benefit of tamoxifen may not yet have been realized in the ATAC trial. But it is important to note the tamoxifen efficacy performance in the ATAC trial was almost identical to the 3.5% annual recurrence rate seen with 3 years' treatment in the 1995 Early Breast Cancer Trialists' Collaborative Group overview analyses, when adjusted for nodal status [6]. Thus the benefits seen with anastrozole can be attributed to improved drug activity rather than to a suboptimal result with tamoxifen. These data demonstrate that, although follow-up from the ATAC trial is <5 years, tamoxifen has shown predictable results, with anastrozole showing improved efficacy over tamoxifen.

In summary, currently available data for anastrozole in the early breast cancer setting could be considered to be as significant as the data first seen with tamoxifen nearly 20 years ago [5]. It is not too early to replace tamoxifen with anastrozole as the first-choice endocrine therapy for the treatment of postmenopausal women with hormone-responsive early breast cancer, although patients treated with anastrozole should be monitored closely in terms of both efficacy and tolerability to ensure that benefits continue beyond the median follow-up of 2.75 years. When 5-year ATAC data become available in around 12 months, we will be able to provide further answers.

5. Aromatase inhibitors in ongoing adjuvant trials

Other adjuvant trials involving anastrozole that are currently underway include ARNO ('Arimidex'—Nolvadex), two Austrian trials (ABCSG 8, ABCSG 6a) in postmenopausal women with hormone receptor-positive breast cancer and the ABCSG 12 trial in premenopausal women with hormone receptor-positive tumours. ARNO ($n = 1000$) and ABCSG 8 ($n = 3500$) are investigating sequential treatment options (5 years of tamoxifen versus 2 years of tamoxifen followed by 3 years of anastrozole treatment). ABCSG 6a ($n = 1700$) compares anastrozole or control for 3 years after 5 years of tamoxifen or tamoxifen and aminoglutethimide treatment. ABCSG 12 compares goserelin treatment for 3 years followed by 3 years of anastrozole or tamoxifen ±3 years of zoledronate (a bisphosphonate) or control.

Letrozole is being compared with tamoxifen in two adjuvant trials (BIG 01-98 and NCIC MA.17). BIG 01-98 is a four-arm trial that is investigating sequential treatment options (2 years of tamoxifen versus 2 years of letrozole followed by 3 years of tamoxifen or letrozole treatment). NCIC MA.17 is a 10-year trial that is investigating the effect of treatment with tamoxifen for 5 years followed by 5 years of placebo versus 5 years of letrozole treatment.

There are currently two trials investigating exemestane as adjuvant treatment for breast cancer. The first is BIG 02-97, in which 5 years of tamoxifen is compared with 2 years with tamoxifen followed by 3 years with exemestane. The other trial, NSABP B33, is a sequencing trial, which will investigate the outcome after 5 years of tamoxifen treatment followed by either 2 years of exemestane treatment or no further treatment.

All of these trials have yet to report their findings and until they do, the data from the ATAC trial, in which anastrozole was used, should not be extrapolated for use with other aromatase inhibitors in the adjuvant setting. Although the extensive body of clinical trial data from the advanced setting for these aromatase inhibitors would suggest that they might be as efficacious as each other, based on the differing pharmacology profiles it is likely that they may have different toxicity profiles. Therefore, until direct data are available, anastrozole is the preferred aromatase inhibitor for use in the adjuvant setting.

6. Conclusion

Anastrozole showed superior efficacy to tamoxifen for DFS, TTR and contralateral breast cancer. Early findings show anastrozole to be an effective and well-tolerated endocrine option for the treatment of postmenopausal patients with early breast cancer. For the first time a choice now exists for adjuvant endocrine treatment for postmenopausal women with hormone responsive tumours. Longer follow-up will further define the benefit/risk of anastrozole adjuvant therapy.

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