available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Clinical decision making in breast cancer: TAM and aromatase inhibitors for older patients - a jungle?

Laura Biganzoli, Sara Licitra, Wederson Claudino, Marta Pestrin, Angelo Di Leo*

'Sandro Pitigliani' Medical Oncology Unit, Hospital of Prato, Tuscany Cancer Institute, Piazza dell'Ospedale, 59100 Prato, Italy

ARTICLE INFO

Article history:
Received 8 March 2007
Received in revised form 18 April 2007
Accepted 2 July 2007
Available online 14 August 2007

Keywords:
Tamoxifen
Aromatase inhibitors
Phase III studies
Breast cancer
Elderly patient

ABSTRACT

Aromatase inhibitors and inactivactors (AIs) have been/are being widely investigated as an alternative to tamoxifen in the treatment of postmenopausal breast cancer patients. In this paper we have reviewed data from phase III studies to define the role of AIs *versus* tamoxifen as first-line therapy in patients with metastatic breast cancer, as primary therapy for not operable or early breast cancers not suitable for conservative surgery and as adjuvant treatment for women with early breast cancer. An effort has been performed to evaluate whether specific recommendations were needed for older postmenopausal patients.

AIs play a key role in the treatment of advanced breast cancer and represent the agent of choice in patients who are candidates to neoadjuvant hormone-therapy. Longer follow-up of already published trials and additional data coming from ongoing studies will better define when and how to use AIs in the adjuvant setting.

For many years, tamoxifen, a selective oestrogen-receptor modulator, represented the standard of care for patients with endocrine sensitive breast cancer. However, in recent years, several studies have suggested that aromatase inhibitors and inactivators (AIs) might be superior to tamoxifen in postmenopausal women both in early and advanced stages of disease. In this manuscript we will review the results of trials comparing tamoxifen with third generation AIs both in terms of efficacy and safety and discuss whether specific recommendations should be made for elderly patients.

1. Metastatic breast cancer

Until the mid 1990s, tamoxifen was the first-line endocrine treatment of choice for postmenopausal patients with hormone-receptor positive advanced breast cancer. Third generation AIs are a class of endocrine agents that act by interfering with aromatisation, a process that converts androgens to oestrogens. The most studied AIs, anastrozole, exemestane, and letrozole, have been directly compared with tamoxifen as first-line treatment for postmenopausal hormone-receptor positive advanced breast cancer women in phase III trials. Results are summarised in Table 1. Two trials, one performed in Europe and the other in North America, compared anastrozole with tamoxifen with conflicting results. The North American trial showed that anastrole was superior to tamoxifen in terms of clinical benefit (CB) and time to tumour progression (TTP).[1] The European trial of similar design failed to confirm these results.[2] Differences in the proportion of patients whose oestrogen-receptor (ER) status was unknown or who had received adjuvant tamoxifen was offered as an explanation of the discordant results. An unplanned, pooled analysis of the two trials showed that anastrozole induced a prolongation in TTP in patients with ER and/or progesterone receptor (PgR) positive tumours.[3] The efficacy of exemestane was compared with that of tamoxifen in the context of the EORTC trial 10951. At a median follow-up of 29 months, exemestane showed significant

* *Corresponding author*: Tel.: +39 574 434766; fax: +39 574 29798.
E-mail address: lbiganzoli@usl4.toscana.it (L. Biganzoli).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.07.007

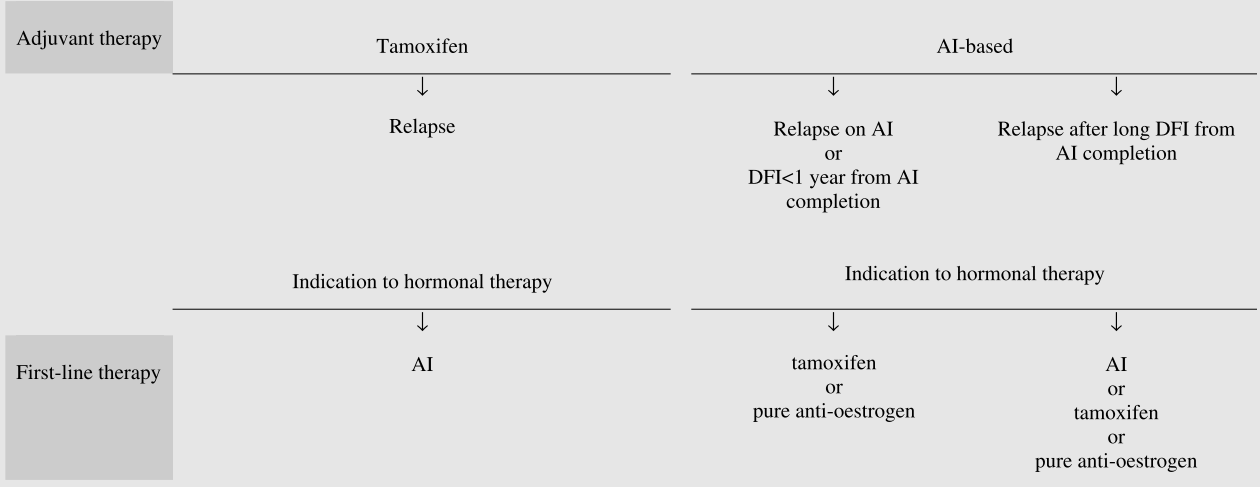
Table 1 – Randomised phase III trials of third-generation aromatase inhibitors *versus* tamoxifen conducted in first-line metastatic breast cancer Patients

Study	Treatment	ER status	No. pts	Endpoints	AI	Tamoxifen	P value
Nabholtz[1]	Anastrozole 1mg/die *versus* Tamoxifen 20 mg/die	ER or PgR+ (88%) or uk	353	RR	21%	17%	NS
				CB	59%	46%	0.009
				TTP	11 mos	5.6 mos	0.005
				OS[6]	39.2 mos	40.1mos	NS
Bonneterre[2]		ER or PgR+ (44%) or uk	668	RR	32%	32%	NS
				CB	56%	55%	NS
				TTP	8 mos	8 mos	NS
				OS			
Bonneterre[3]		Pooled results	1021	RR	29%	27%	NS
				CB	57%	52%	NS
				TTP	8.5 mos	7 mos	NS
				TTP[a]	10.7 mos	6.4 mos	0.02
				OS			
Paridaens[4]	Exemestane 25 mg/die *versus* Tamoxifen 20 mg/die	ER+ or uk if DFI > 2years	382	RR	46%	31%	0.005
				CB	66%	49	
				TTP	9.9 mos	5.8 mos	0.02
				OS			NS
Mouridsen[5]	Letrozole 2.5 mg/die *versus* Tamoxifen 20 mg/die	ER and/or PgR+ or uk	916	RR	32%	21%	0.0002
				CB	50%	38%	0.0004
				TTP	9.4 mos	6 mos	<0.0001
				OS	34 mos	30 mos	NS

Empty blanks = data not reported; ER+, oestrogen receptor positive; PgR+, progesterone receptor positive; uk, unknown; DFI, disease-free interval; RR, response rate; CB, clinical benefit; TTP, time to progression; OS, overall survival; NS, not significant.
a Oestrogen and/or progesterone receptor positive tumours (60% of combined trial population).

superiority over tamoxifen in terms of RR and progression-free survival (PFS).[4] In the largest phase III trial, letrozole was compared to tamoxifen. At a median follow-up of 32 months, letrozole was shown to be superior to tamoxifen in terms of response rate (RR), CB and TTP.[5] Time to worsening of Karnofsky performance score was significantly delayed with letrozole compared with tamoxifen ($P = 0.001$). Of note, none of the above mentioned trials showed an advantage in terms of overall survival (OS) in favour of the AIs.[1–6] Recently, Mauri and colleagues performed a meta-analysis of randomised controlled trials that compared several generations of AIs with standard hormonal treatment in patients with advanced

Table 2 – Algorithm for first-line endocrine therapy in postmenopausal metastatic patients



DFI, disease-free interval

disease.[7] With the limitation of a meta-analysis based on data collected from published literature, the authors concluded that first-line therapy with third-generation AIs results in a moderate, but statistically significant, prolongation of OS over tamoxifen (11% relative hazard reduction, 95% CI = 1% to 19%; $P = 0.03$).

Overall, the results of the phase III trials comparing a third-generation AI with tamoxifen showed an efficacy to toxicity ratio in favour of the AIs. The most frequently reported side effects on AIs were hot flashes and diarrhoea. In particular, due to the limited period on treatment, no evidence of higher incidence of fractures on AIs *versus* tamoxifen was described. In the letrozole trial, the reported fracture rate per patient-year of treatment was 0.0427 for the AI and 0.0451 for tamoxifen.[5]

Based on these results, and because in metastatic patients with endocrine sensitive tumours, sequential hormonal strategies are used, AIs are nowadays considered the first-line endocrine treatment of choice for postmenopausal patients. In addition, AIs appear to be cost-effective when compared with tamoxifen as first-line hormonal therapy in the United States, United Kingdom, and Canada health systems.[8]

Nowadays, an increasing percentage of postmenopausal patients are being/will be treated with AIs in the adjuvant setting. An algorithm for first-line endocrine therapy in postmenopausal metastatic patients that takes into account treatment received in the adjuvant setting is proposed in Table 2.

No specific recommendations are due for older patients. Limited data suggest that a treatment with AIs is feasible also in an elderly breast cancer population with comorbidities and disabilities.[9] A total of 45 women, aged 65 to 93 years, affected by a moderate to severe degree of comorbidity and disability measured by a comprehensive geriatric assessment scale, were treated with formestane, a selective steroidal AI, without evidence of any worsening in pre-existing comorbidities, especially hypertension and vascular diseases.

2. Early or locally advanced breast cancer: neoadjuvant therapy

In the last few years, data have been reported from randomised trials that compared an AI with tamoxifen as neoadjuvant treatment for postmenopausal women with endocrine sensitive breast cancer. Population characteristics and results are given in Table 3. Anastrozole was compared with tamoxifen, both given for a total period of 3 months in the Pre-Operative Arimidex Compared to Tamoxifen (PROACT) and Immediate Preoperative Arimidex Tamoxifen or Combined with Tamoxifen (IMPACT) trials.[10,11] Neoadjuvant chemotherapy was allowed in the PROACT study but was an exclusion criterion in IMPACT. In both trials no significant difference in terms of RR was observed between the two treatment arms while the use of the AI resulted in a higher breast conserving surgery (BCS) rate. This higher conversion rate to BCS was observed in the IMPACT trial only among patients deemed by their surgeon to be eligible for BCS after treatment. Semiglazov and colleagues treated a total of 152 women with 3 months of either exemestane or tamoxifen.[12] Clinical RR was higher in patients receiving the AI with no differences in radiological RR between the two treatment arms. Also in this study, therapy with AI was associated to a higher rate of BCS. A total of 337 breast cancer patients who were not candidates to BCS were treated with 4 months of letrozole or tamoxifen in the context of a double-blind randomised trial.[13] Letrozole did significantly better than tamoxifen in terms of RR (clinically and radiologically assessed) and in terms of BCS rate. Differences in RR between letrozole and tamoxifen were most marked for tumours that were positive for ErbB-1 and/or ErbB-2 and ER (88% *versus* 21%, $P = 0.0004$).[14] These data are not confirmed with prolonged treatment with AIs in the adjuvant setting. Recently, Dowsett and colleagues looked at the relationship between quantitative ER/PgR, HER-2 status and recurrence in the anastrozole alone or in combination with tamoxifen *versus* tamoxifen alone (ATAC) trial,

Table 3 – Randomised trials of third-generation aromatase inhibitors *versus* tamoxifen given as neoadjuvant therapy for endocrine sensitive breast Cancer

Study	Treatment	Population	No. pts	Endpoints	AI	Tamoxifen	P value
Smith[10]	Anastrozole *versus* Tamoxifen	Large operable (>2cm) tumours; HR+	220	Clinical RR	37%	36%	0.53
				Ultrasound RR	24%	20%	0.87
				BCS[b]	46%	22%	0.03
Cataliotti[11]		Large operable or potentially operable locally advanced tumours; HR+	314[a]	Clinical RR	50%	46%	0.07
				Ultrasound RR	39.5%	35.%	0.08
				BCS ‘	43%	31%	0.04
Semiglazov[12]	Exemestane *versus* Tamoxifen	T1–4, N1–2, M0; ER+	151	Clinical RR	76.%	40%	0.05
				Ultrasound RR	60.5%	37%	0.092
				Mammographic RR	64%	37%	0.082
				BCS	37%	20%	0.05
Eiermann[13]	Letrozole *versus* Tamoxifen	T2–4, N0–2, M0 inoperable (14%) or not suitable for conservative surgery; HR+	337	Clinical RR	55%	36%	<0.001
				Ultrasound RR	35%	25%	0.042
				Mammographic RR	34%	16%	<0.001
				BCS	45%	35%	0.022

HR+, hormonal receptor positive; ER+, oestrogen receptor positive; RR, response rate; BCS, breast-conserving surgery.
a Patients treated with hormonal therapy only.
b Patients deemed by their surgeon to be eligible for BCS after treatment.

and showed that ER, PgR and HER-2 were not identified as predictive factors for differential benefit between anastrozole and tamoxifen.[15] Globally, independently from the HER-2 status of the tumour, hormonal therapy with AIs is to be preferred to tamoxifen due to the consistent evidence of increased BCS rate. This is extremely important for elderly patients who are unfit or at high risk for general anaesthesia. In these patients tumour down-staging could allow less extensive surgery under local anaesthesia. Due to the absence of data in favour of AIs in terms of long-term outcome, tamoxifen represents a reasonable option in presence of contraindications to AIs or in countries in which economical aspects represent an important issue.

3. Early breast cancer: adjuvant setting

Five years of adjuvant therapy with tamoxifen has for several years represented the gold standard for patients with endocrine sensitive early breast cancer. The role of tamoxifen, in postmenopausal women, has been challenged in the last few years by the results of clinical trials evaluating the role of AIs in the adjuvant setting. These trials can be grouped, according to the modality of introduction of the AI in the treatment programme, as: 1. Upfront adjuvant therapy trials, in which there is a head to head comparison between tamoxifen and the AI; 2. Switching trials, in which 5 years of therapy with tamoxifen is compared with tamoxifen for 2–3 years followed by AI for a global duration of 5 years. The alternative sequence, AI followed by tamoxifen, has also been investigated in one randomised trial; 3. Extended adjuvant trials, evaluating the benefit of an AI after 5 years of tamoxifen. Study design and results of published trials are summarised in Table 4 and will be discussed in this paper.

3.1. *Upfront trials*

In the ATAC trial, a total of 9366 postmenopausal patients who were eligible to receive adjuvant endocrine therapy were randomised to receive tamoxifen, anastrozole or a combination of tamoxifen plus anastrozole for 5 years.[16] Patients' median age was 64 years. While results with the combination were not significantly different from those with tamoxifen alone, at a median follow-up of 68 months, single agent anastrozole significantly prolonged disease-free survival (DFS), time to recurrence (TTR) and time to distant recurrence (TDR) over tamoxifen .[17] No difference was observed in terms of overall survival (OS) between the two agents.

A total of 4922 postmenopausal women with receptor-positive breast cancer have been randomised (double-blind) in the context of the Breast International Group (BIG) study 1–98, to 5 years of tamoxifen or letrozole.[18] Patients median age was 61 years, range 38–90. At a median follow-up of 51 months, patients on letrozole presented a longer DFS, TTR and TDR than patients on tamoxifen.

3.2. *Switching trials*

In the Intergroup Exemestane Study (IES) 4724 postmenopausal women with ER-positive or ER-unknown breast cancer,

Table 4 – Trials evaluating the role of aromatase inhibitors in the adjuvant setting

Study (No. patients)	Study design	Follow-up months	Endpoints							
Upfront adjuvant therapy										
ATAC[17] (*n*=6241)	5 y A / 5 y T	68	DFS TTR	HR 0.87; *P*=0.01 HR 0.79; *P*=0.0005	TDR	HR 0.86; *P*=0.04	OS	HR 0.97; *P*=0.2		
BIG 1–98[18] (*n* =4922)	5 y L / 5 y T	51	DFS TTR	HR 0.82; *P*=0.007 HR 0.78; *P*=0.004	DDFS TDR	HR 0.87; *P*=0.07 HR 0.81; *P*=0.03	OS	HR *P*=0.35	0.91;	
Switching trials										
IES[19] (*n* =4724)	2–3y T / 2–3y T 2–3y T / 2–3y T	55.7	DFS	HR 0.75; *P*=0.0001	TDR	HR 0.83; *P*=0.03	OS	HR *P*=0.07	0.85;	
ABCSG8/ ITA/ ARNO95[20] (*n* =4600)	2–3y T / 2–3y A 2–3y T / 2–3y T	30	DFS	HR 0.59; *P*<0.0001	DDFS	HR 0.61; *P*=0.002	OS	HR *P*=0.04	0.71;	
Extended adjuvant therapy										
MA 17[22] (*n* =5187)	5y T / 5 y L 5y T / placebo	30	DFS	HR 0.58; *P*<0.001	DDFS	HR 0.60; *P*<0.002	OS	HR *P*=0.3	0.82;	
ABCSG 6a[23] (*n* =856)	5y T+/–AG / 3 y A 5y T+/–AG / NT	60	DFS	HR 0.64; *P*=0.047			OS	NS		

A, anastrozole; T, tamoxifen; L, letrozole; E, exemestane; NS, not significant; HR, hazard ratio; y, years; AG, aminoglutethimide;DFS, disease-free survival; TDR, time to distant recurrence; OS, overall survival; TTR, time to recurrence; DDFS, distant disease-free survival.

who were disease-free on 2–3 years of tamoxifen, were randomly assigned to switch to exemestane or continue tamoxifen for the remainder of 5 years of treatment.[19] Patients' median age was 64 years. At a median follow-up of 55.7 months, patients who switched to exemestane presented an advantage in terms of DFS and TDR. A small advantage in terms of OS was observed in favour of exemestane when 122 patients originally reported as ER unknown and later found to be ER-negative were excluded from the efficacy analysis (HR 0.83, $P = 0.04$).

Results have recently been published of a meta-analysis of three clinical trials, the Austrian Breast and Colorectal Cancer Study Group (ABCSG 8), Arimidex-Nolvadex (Arno 95) and the Italian Tamoxifen Anastrozole (ITA) studies, in which postmenopausal women with hormone-sensitive early breast cancer were randomised to anastrozole after 2–3 years of tamoxifen or continued to take tamoxifen.[20] A total of 4600 eligible patients were included in the meta-analysis. Median patient age was 63 years. After a median follow-up of 30 months, there was a significant reduction in the DFS hazard rate and in the risk of death.

3.3. *Extended adjuvant trials*

The NCIC CTG MA.17 study targeted postmenopausal women with primary breast cancer who had completed approximately 5 years of adjuvant tamoxifen therapy.[21] A total of 5187 patients were randomised to receive (double-blind) either letrozole or placebo for 5 years. Patients' median age was 62 years, 25% of the patients were aged $\geqslant$ 70 years. The study was interrupted and unblinded after the first interim analysis due to the clear advantage in terms of DFS with letrozole. At a median follow-up of 30 months, extended therapy with letrozole resulted in prolonged DFS and DDFS.[22] A subgroup analysis also showed an advantage in terms of OS among node-positive patients (HR 0.61; $P = 0.04$). After the unblinding, patients in the placebo arm were offered letrozole. The results of an intent to treat analysis (ITT) performed after a median follow up of 74 months was presented at the American Society of Clinical Oncology (ASCO) meeting in 2006.[23] In the ITT analysis, patients originally randomised to receive letrozole did better than patients originally randomised to placebo in terms of DFS (4y DFS HR = 0.64; $P = 0.00002$) and DDFS (4y DDFS HR = 0.76; $P = 0.041$) despite 73% of the patients on placebo switching to letrozole after unblinding.

In the study ABCSG-6a, a total of 456 postmenopausal women who had received, in the context of trial ABCSG6, either 5 years of tamoxifen or tamoxifen plus aminoglutethimide for a 2 year period followed by 3 years of tamoxifen alone, were re-randomised to switch to anastrozole or no treatment for a further 3 years.[24] Patients' median age was 61.8 years. At a median follow-up of 60 months, significantly fewer patients in the AI group experimented disease recurrence compared with the no treatment group.

Briefly, all the above-discussed trials showed that AIs were superior to tamoxifen in reducing the risk of tumour relapse. Based on the early results of these trials, the Panel of the ASCO technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer concluded that the optimal adjuvant hormonal therapy, in this subgroup of patients, should include an aromatase inhibitor.[25]

An unresolved question is whether it is more beneficial for the patient to receive an AI upfront or to start with tamoxifen and then shift to an AI. A clear answer to this dilemma will emerge from two trials, the BIG 1–98 and the Tamoxifen Exemestane Adjuvant Multinational (TEAM), which investigate upfront AI *versus* AI after tamoxifen.

Can the results observed in the general 'postmenopausal' population be transferred to older women?

Except for the ABCSG8 and ARNO 95 trials, there was no age limit for study entry; patients' median age was between 61 and 64 years. No impact of age on DFS was observed in the upfront or switching trials. Detailed results for the BIG 1–98, IES and combined analysis of the ABCSG8/ ARNO95 trials are given in Table 5.[18,19,26] Apparently, as already shown for tamoxifen,[27] older patients derive the same benefit from AI as younger patients. Regarding the extended adjuvant strategy, Muss and colleagues divided patients randomised in the MA 17 into three age-groups: younger than 60 (<60), 61–69, and 70 years old and older (70+).[28] There was no age-related difference in DFS or DDFS for the overall study population. OS was significantly shorter in 70+ patients probably due to competing causes of death. However, a significant improvement in OS on letrozole was observed for 70+ patients with node-positive breast cancer ($P = 0.04$). At 4 years, subgroup analyses by age comparing DFS for letrozole and placebo showed statistically significant benefit only in the <60 subgroup, even if the hazard ratios for all subgroups were in favour of letrozole (Table 6). Based on these data an extended adjuvant approach can be recommended

Table 5 – Per age subgroup analysis for disease-free survival

Study	Follow-up	Age group	*n*	HR	95% CI	P
BIG 1–98[18]	51 months	<65	3127	0.82	0.67–0.99	0.04
		65+	1795	0.82	0.67–1.01	0.06
IES[19]	55.7 months	<60	1523	0.82	0.63–1.06	NR
		60–69	2021	0.70	0.56–0.87	NR
		70+	1180	0.81	0.63–1.04	NR
ABCSG8/ARNO95[26]	28 months	<60	1265	0.63	0.40–1.00	0.05
		60+	1959	0.58	0.39–0.87	0.007

Table 6 – MA.17 study: per age subgroup analysis comparing letrozole and placebo at 4-years for disease-free survival and overall survival

Group	Disease-free survival				Overall survival			
	Letrozole	Placebo	HR	P	Letrozole	Placebo	HR	P
< 60	94.5	90.2	0.46	0.0004	97.6	97.3	0.78	0.56
61–69	93.8	89.1	0.68	0.078	96.7	95.8	0.75	0.56
70+	94.7	90.2	0.67	0.12	90.8	90.6	0.82	0.44

also for healthy 70+ women with high risk, i.e. node-positive breast cancer.

Aging is associated with an increased incidence and prevalence of comorbidities and the presence of specific illnesses might drive the choice between tamoxifen and AIs in this population. Therefore, safety issues are extremely important in older patients.

The long-term safety profile of tamoxifen is well known. In comparison with AIs, tamoxifen is associated with a higher risk of endometrial cancer and thromboembolic events such as deep venous thrombosis, pulmonary embolism, and cerebrovascular accidents. Among the side effects described with AIs, osteoporosis, bone fracture and cardiac events are particularly worrisome for older patients.

Variation in bone mineral densitometry (BMD), incidence of osteoporosis, and bone fracture in patients treated in AIs adjuvant trials, are described in Table 7. Briefly, the introduction of AI in the adjuvant setting was associated to an increased incidence of osteopenia and osteoporosis. With the exception of MA.17, therapy with AIs was also associated with a significant increase in clinical fracture. Preliminary data from IES suggest that there is no significant effect of age on the risk of fracture.[29] Women receiving AIs should be monitored for osteoporosis risk to allow for early intervention and patients who develop osteoporosis should receive bisphosphonates. In the United States, 26% of women aged 65 years and older and more than 50% of women aged 85 and older have osteoporosis.[30] No data exist on BMD changes in patients with pre-existing osteoporosis on AIs. Whilst waiting for data proving that bisphosphonates are an effective treatment for osteoporosis in the presence of an AI, tamoxifen should be generally considered the agent of choice in this group of patients.

A higher incidence of cardiovascular events (CV) with AIs has been reported in some adjuvant trials. Detailed information is available for the ATAC, BIG 1–98, IES and MA.17 trials (Table 8). In the ATAC trial, apart from a non-statistically significant difference in angina, the occurrence of other ischemic CV events was similar between tamoxifen and anastrozole.[31] In the BIG 1–98 trial, although the overall incidence of cardiac adverse events did not differ significantly between the two treatments, a trend for higher grade (3 to 5) cardiac events on letrozole compared with tamoxifen was seen.[18] In particular, double the number of cardiac deaths was reported with letrozole *versus* tamoxifen. In the IES trial, there was a trend for higher incidence in myocardial infarctions (MI) on exemestane. Of note, the effects of treatment on the risk of MI seemed largely restricted to patients with a history of hypertension. Seventy-one percent of patients on exemestane who had MI had hypertension at baseline compared with 32% of the corresponding patients on tamoxifen.[19] A less extensive evaluation of CV problems was performed in the ABCSG8, the ARNO95 and the ITA trials; no difference in MI and CV events in patients switching to anastrozole compared with those who continued tamoxifen were reported in the ABCSG8/ARNO95 combined analysis and ITA trial, respectively.[26,32]

Apart from the BIG 1–98 trial, that showed that patients on letrozole experienced more CV events other than ischemia and cardiac failure and more severe cardiac events, no significant differences in terms of CV events were observed in all the other adjuvant trials. Extremely interesting are the data from the MA.17 trial in which the AI was compared with placebo. The fact that no difference in terms of CV events was reported in this trial suggests that the cardioprotective effect of tamoxifen may be the principle driving factor for difference in cardiac toxicity observed in all adjuvant trials when an AI is compared to tamoxifen. A longer follow up will probably better clarify the safety profile of letrozole. For the time being conclusions regarding the relationship between AIs and cardiac risk are limited by the modest number of events reported. Additional data coming from the study MA.17 show that acute toxicities by age for letrozole and placebo were not different in 70+ patients (Table 9).[28] In addition, in this

Table 7 – Bone toxicities from published adjuvant trials

Events	ATAC			BIG 1-98			ABSG8/ARNO 95			ITA			IES			MA.17		
%	A	T	P	L	T	P	A	T	P	A	T	P	E	T	P	L	P	P
Bone fracture	11.0	7.7	<0.0001	8.6	5.8	<0.001	2	1	0.015	1.0	1.3	0.6	4.3	3.1	0.03	5.3	4.6	0.25
Osteoporosis													7.3	5.5	0.01	8.1	6.0	0.003
BMD changes -lumbar spine	from baseline to 5 yrs												at 24 months			at 24 months		
	–8.1		<0.0001										–4.0			–5.4		0.008

Empty blanks = data not reported; A, anastrozole; T, tamoxifen; L, letrozole; E, exemestane; BMD, bone mineral densitometry.

Table 8 – Details on cardiovascular events from ATAC, BIG 1-98, IES and MA.17 trials

Adverse Events	ATAC			BIG 1-98			IES			MA.17		
	A no. (%)	T no. (%)	P	L no. (%)	T no. (%)	P	E no. (%)	T no. (%)	P	L no. (%)	P no. (%)	P
All patients	3092	3094		2448	2447		2320	2338		2572	2577	
Cardiovascular events[a,b,c]				134 (5.5)	122 (5.0)	0.48[d]	382 (16.5)	350 (15.0)	0.16	149 (5.8)	144 (5.6)	0.76
- ischemic events	127 (4)	104 (3)	0.1	54 (2.2)	41 (1.7)	0.21	185 (8.0)	162 (6.9)	0.17			
- myocardial infarction	37 (1)	34 (1)	0.7				31 (1.3)	19 (0.8)	0.08	9 (0.3)	11 (0.4)	
- angina[e]	71 (2)	51 (2)	0.07							31 (1.2)	23 (0.9)	
- cardiac failure				24 (1)	14 (0.6)	0.14						
- cerebrovascular events	62 (2)	88 (3)	0.03	34 (1.4)	35 (1.4)	0.9				17 (0.7)	15 (0.6)	
- thromboembolic events[f]	87 (3)	140 (5)	0.0004	50 (2)	94 (3.8)	<0.001	28 (1.2)	54 (2.3)	0.004	11 (0.4)	6 (0.2)	
- other CV events[g]				19 (0.8)	6 (0.2)	0.014						
Deaths due to CV events[h]	49 (2)	46 (1)										
Deaths due to cardiac events				11	5		14	13				
Deaths due to vascular events							17	11				
Deaths due to CBV events	14 (<1)	22 (1)										

Empty blanks = data not reported; A, anastrozole; T, tamoxifen; L, letrozole; E, exemestane; CV, cardiovascular; CBV, cerebrovascular.

a BIG 1–98: included ONLY cardiac events.

b IES: cardiovascular events excluded venous thromboembolic events.

c MA.17: cardiovascular events included thromboembolic and cerebrovascular events.

d Fisher's exact $P < 0.001$ for incidence of grade 3 to 5 cardiac events.

e MA.17: angina = new or worsening angina.

f ATAC and IES: venous thromboembolic events.

g Included cardiovascular disorders not otherwise specified, aneurysm, aortic aneurysm rupture, aortic dilation, aortic stenosis, arteriosclerosis, atherosclerosis (obliterans), femoral arterial stenosis, hypertensive angiopathy, iliac artery stenosis, and intermittent claudication.

h Included myocardial infarction, myocardial ischemia, arteriosclerosis, coronary-artery disorder, coronary thrombosis, peripheral vascular disorder, heart arrest, arrhythmia, atrial flutter, cardiomyopathy, congestive heart failure, embolus, heart failure, sudden death, left-heart failure, lung oedema, mesenteric occlusion, occlusion, hypertension, hypotention, haemorrhage, and vascular anomaly.

Table 9 – Acute toxicities versus treatment and age including only toxicity with difference of P < 0.05

	Letrozole (%)	Placebo (%)	P
Age <60 years (*n* = 2152)			
Arthralgia	27	19	<0.0001
Myalgia	15	12	0.03
Vaginal Bleeding	8	12	0.007
Age 60–69 years (*n* = 1694)			
Hot flushes	59	52	0.0027
Insomnia	7	4	0.014
Arthralgia	26	20	0.005
Alopecia	5	3	0.03
Age ⩾ 70 (*n* = 1323)	No difference among letrozole and placebo		

subgroup of patients, the administration of letrozole did not have a negative impact on quality of life at 36 months.[28]

4. Conclusions

AIs are nowadays considered the first-line endocrine treatment of choice for postmenopausal patients with endocrine sensitive breast cancer even if their increasing use in the adjuvant setting opens discussions on which is the optimal endocrine agent to be used in case of tumour relapse. There are no specific age related safety concerns related to the use of AIs in older patients with metastatic disease.

Due to the consistently reported increased BCS rates *versus* tamoxifen, AIs represent the recommended class of agents to be used in patients who are candidates for neoadjuvant endocrine therapy, although tamoxifen may be a reasonable option in various situations. Primary therapy with an AI is strongly recommended in older patients who are not candidates for BCS and are not fit enough to have surgery under general anaesthesia.

Less well defined is the use of AIs in the adjuvant setting. Waiting for the results of ongoing trials and longer follow-up of published trials, a third-generation AI should be offered to postmenopausal patients with significant risk of tumour relapse. Based on the ATAC and BIG 1-98 data that respectively showed an early advantage in terms of DFS in favour of the AI and a significant benefit in DFS only in node positive patients, upfront AIs should be considered for patients at risk of an early relapse, i.e. patients with node positive (i.e. 4+) and/or large tumours. Tamoxifen remains a valuable option for early breast cancers at low risk of relapse, i.e. T < 1 cm, grade 1, low proliferative index. In-between patients might be good candidates for sequential treatment.

An extended adjuvant treatment with an AI found its rationale on evidences of a relatively constant risk of tumour relapse for ER-positive tumours over time.[33] Individualised estimates of the risk of relapse and death after 5 years of tamoxifen based on standard pathologic prognostic markers suggest that extended adjuvant treatment could be avoided in women at low-risk of relapse.[34] A subgroup analysis of the MA.17 trial showed that this 'prolonged' approach is also effective in healthy 70+ women with high risk breast cancer.

Among AI-related side effects, bone problems are the most worrisome for older patients due to the increasing incidence of osteoporosis and fracture risk with age in the general population. In the Zometa–Femara Adjuvant Synergy Trial, a total of 602 postmenopausal women with early breast cancer, receiving adjuvant letrozole for 5 years, were randomised to either upfront or delayed-start (at the decrease of lumbar spine or total hip scores to less than –2.0 or at the occurrence of a nontraumatic fracture) zoledronic acid, given at the dose of 4 mg every 6 months.[35] With 1-year of follow-up, upfront treatment has shown to prevents bone loss. A longer follow-up is needed to determine whether the bone loss observed in the delayed group can be stabilised or restored to baseline values with the administration of the bisphosphonate. Waiting for these data, adjuvant therapy with AIs should not generally be proposed to patients with osteoporosis. Specific cost/effectiveness evaluations should be performed in case of high-risk patients.

Biases in patients' selection criteria are often described to explain the reduced participation of elderly patients in clinical trials.[36] With the term 'elderly' we define a population that is extremely heterogeneous in terms of comorbidities and disabilities, and as a consequence, in terms of life expectancy and tolerability to medications. Detailed information on older women entered in the AIs adjuvant trials are therefore needed to know whether the general considerations on the role of these agents in the adjuvant setting can also be transferred to both the unfit elderly and to the oldest elderly. Up to date, no data are available on the efficacy and safety profile of adjuvant AIs in frail and very elderly patients.

Conflict of interest statement

Dr. Biganzoli has received lecture fees from Astra Zeneca and Pfizer; Dr. Di Leo has received lecture fees from Astra Zeneca and Novartis and also lecture fees and an educational grant from Pfizer. Drs. Licitra, Claudino, and Pestrin: None declared.

REFERENCES

1. Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol* 2000;**18**:3758–67.
2. Bonneterre J, Thurlimann B, Robertson JFR, et al. Anastrozole *versus* tamoxifen as first-line therapy for advanced breast carcinoma in postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficay and Tolerability study. *J Clin Oncol* 2000;**18**:3748–57.
3. Bonneterre J, Buzdar A, Nabholtz JM, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer* 2001;**92**:2247–58.
4. Paridaens R, Therasse P, Dirix L, et al. First line hormonal treatment (HT) for metastatic breast cancer (BMC) with exemestane (E) or tamoxifen (T) in postmenopausal patients (pts) : a randomized phase III trial of the EORTC Breast Group. *J Clin Oncol* 2004;**22**(14S). abstract 515.
5. Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole *versus* tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival

and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003;**21**:2101–9.
6. Nabholtz JM, Bonneterre J, Buzdar A, Robertson JF, Thurlimann B. Anastrozole (Arimidex) *versus* tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. *Eur J Cancer* 2003;**39**:1684–9.
7. Mauri D, Pavlidis N, Polyzos NP, Ioannidis JPA. Survival with aromatase inhibitors and inactivators *versus* standard hormonal therapy in advanced breast cancer: meta-analysis. *J Natl Cancer Inst* 2006;**98**:1285–91.
8. Karnon J. Aromatase inhibitors in breast cancer: a review of cost considerations and cost effectiveness. *Pharmacoeconomics* 2006;**24**:215–32.
9. Venturino A, Comandini D, Granetto C, et al. Formestane is feasible and effective in elderly breast cancer patients with comorbidity and disability. *Breast Cancer Res Treat.* 2000;**62**:217–22.
10. Smith I, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *on behalf of IMPACT trialists. J Clin Oncol.* 2005;**23**:5108–16.
11. Cataliotti L, Buzdar A, Noguchi S, et al. Comparison of anastrozole *versus* tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: the Pre-Operative Arimidex" Compared to Tamoxifen (PROACT) trial. *Cancer* 2006;**106**:2095–103.
12. Semiglazov VF, Kletsel A, Semiglazov VV, et al. Exemestane (E) vs Tamoxifen (T) as neoadjuvant endocrine therapy for postmenopausal women with ER+ breast cancer (T2N1-2, T3N0-1,T4N0M0). *J Clin Oncol* 2005;**23**(16S):530.
13. Eiermann W, Paepke S, Appfelstaedt J, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. *Ann Oncol* 2001;**12**:1527–32.
14. Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. *J Clin Oncol* 2001;**19**:3808–16.
15. Dowset M, Allred DC, et al. Relationship between quantitative ER and PgR expression and HER2 status with recurrence in the ATAC trial. *Breast Cancer Res Treat* 2006;**100**(Suppl 1):S21. abstract 48.
16. The ATAC Trialists' Group. Anastrozol alone or in combination with tamoxifen *versus* tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;**359**:2131–9.
17. ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;**365**:60–2.
18. Coates AS, Keshaviah A, Thurlimann B, et al. Five years of letrozole compared with tamoxifen as initial therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. *J Clin Oncol* 2007;**25**:486–92.
19. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane *versus* tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomized controlled trial. *Lancet* 2007;**369**:559–70.
20. Jonat W, Gnant M, Boccardo F, et al. Effectiveness of switching from adjuavant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early stage breast cancer: a meta-analysis. *Lancet* 2006;**7**:991–6.
21. Goss PE, Ingle JN, Martino S, et al. A randomised trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003;**349**:1793–802.
22. Goss PE, Ingle JN, Martino S, et al. Randomised trial of letrozole following tamoxifen as adjuvant therapy in receptor-positive breast cancer: update findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;**97**:1262–71.
23. Ingle J, Du T, Shepherd L, Palmer M, Pater J, Goss P. NCI CTG MA.17: Intent to treat analysis (ITT) of randomized patients after a median follow-up of 54 months. *J Clin Oncol* 2006;**24**(15S). abstract 549.
24. Jakesz R, Samonigg H, Greil R, et al. Extended adjuvant treatment with anastrozole: results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a). *J Clin Oncol* 2005;**23**(10S). abstract 527.
25. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol.* 2005;**23**:619–29.
26. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anstrozole after 2 years' adjuvant tamoxifen : combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005;**366**:455–62.
27. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**365**:1687–717.
28. Muss HB, Tu D, Ingle JN, et al. The benefits of letrozole in postmenopausal women with early stage breast cancer who have had five years of tamoxifen are independent of age. *Breast Cancer Res Treat* 2006;**100**(Suppl 1):S23. abstract 102.
29. Coleman RE, Banks LM, Girgis SI, et al. Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomized controlled study. *Lancet* 2007;**8**:119–27.
30. Gass M, Dawson-Hughes B. Preventing osteoporosis-related fracture: an overview. *Am J Med* 2006;**119**(Suppl 1):S3–S11.
31. The Arimidex Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. *Lancet Oncol* 2006;**7**:633–43.
32. Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole *versus* continued tamoxifen treatment of early breast cancer/ preliminary results of the Italian Tamoxifen Anastrozole Trial. *J Clin Oncol* 2005;**23**:5138–47.
33. Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. *J Clin Oncol* 1996;**14**:2738–46.
34. Kennecke HF, Olivotto IA, Speers C, et al. Late risk of relapse and mortality among postmenopausal women with estrogen responsive early breast cancer after 5 years of tamoxifen. *Ann Oncol* 2007;**18**:45–51.
35. Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol* 2007;**25**:829–36.
36. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol.* 2003;**21**:1383–9.