The similarities of aromatase inhibitors outweigh the differences

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Although the aromatase inhibitors (AIs) as a class exhibit clear differences in terms of their structure and mechanism of action, these differences do not always translate into clinically significant differences in patient outcomes. In fact, these differences may actually reflect differences in clinical trial design (i.e. upfront, sequential or switch therapy) or the patient population studied. The results of clinical trials demonstrate a clear superiority of third-generation AIs over tamoxifen. It will, however, be necessary to wait for the results of the ongoing head-to-head MA.27 and Novartis trials to determine whether there is any differentiation between the various third-generation AIs. *Anti-Cancer Drugs* 19 (suppl 2): S7–S9 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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It has been contended that the similarities between the various aromatase inhibitors (AIs) by far outweigh the differences. Furthermore, small differences between the AIs in terms of clinical outcomes may perhaps reflect clinical trial design and the patient populations studied.

Although there are clear differences between the AIs in terms of molecular structure, this does not always translate into differences in clinical outcomes. There are two types of antiaromatase agents, which differ structurally and in their mechanism of action [1]. The steroidal inactivator exemestane is structurally similar to androstenedione, the natural substrate of aromatase. Exemestane irreversibly inactivates aromatase, resulting in lower levels of oestrogen [2]. Letrozole and anastrozole are nonsteroidal agents that reversibly inhibit aromatase.

The proportion of peripheral aromatase inhibition among these agents varies from 91.9% for formestane to 98.9% for letrozole and the residual inhibition ranges from 1.1 to 8.1% for letrozole versus formestane [3,4]. It is, however, unclear whether these differences can be translated into meaningful clinical differences.

The major clinical trials differ with regard to randomization procedures: the upfront trials randomize patients after surgery, and the sequential and switching trials randomize patients at a later stage. In the Intergroup Exemestane Study (IES), for example, patients who remained disease-free after 2–3 years of tamoxifen use entered the trial and were randomized to stay on tamoxifen or switch to the steroidal AI exemestane [5]. Therefore, this was a selected population that excluded patients with early recurrence and higher-risk disease, thereby only including patients with more endocrine-responsive disease. In the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 08/Arimidex–Nolvadex (ARNO) 95 combined analysis [6] and the Breast International Group (BIG) 1-98 study [7], patients were randomized upfront to tamoxifen for 5 years or a tamoxifen/AI (or AI/tamoxifen in the case of BIG 1-98) strategy.

When interpreting the results of these trials, it is important to bear in mind the different patient populations being investigated. As these trials are recruiting different patient populations, differences in outcomes are likely to result from different treatment schedules rather than actual differences between the AIs [5–9].

These trials also differ in terms of their defined primary endpoints; disease-free survival (DFS) was the composite of breast cancer recurrence, contralateral breast cancer, all-cause mortality and other first cancer in the BIG 1-98 trial [7], whereas the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [8] only measured the composite of breast cancer recurrence, contralateral breast cancer and all-cause mortality.

In the two upfront trials (ATAC and BIG 1-98), the endpoints are sufficiently similar to draw some valid conclusions with regard to statistical outcomes (Table 1) [5–9]. Of note, the statistical analyses in the switching trials (IES and ARNO) suggested a better clinical outcome in terms of DFS than in the upfront trials. A direct comparison of the outcomes of these switching studies to the upfront trials, however, is not possible given that these trials represented different patient populations. The patients in the IES trial were more endocrine responsive potentially resulting in the lower hazard ratios (HR) observed in the AI patient cohort.

Subgroup analyses (e.g. node-positive, node-negative, chemotherapy pretreatment) from these trials yielded

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differing results regarding the superiority of AIs compared with tamoxifen. In the ATAC trial, there was a DFS advantage for anastrozole over tamoxifen in the node-negative subgroup [8]. In contrast, in the BIG 1-98 study, there was a DFS advantage for letrozole in the node-positive subgroup [7].

In the large clinical trials, most of these analyses were preplanned or retrospective, and patients were not stratified according to subgroup before randomization; therefore these subgroup analyses must be viewed with caution. On the basis of the available data it cannot be concluded that the AIs have different activity.

A retrospective analysis of the ATAC study demonstrated a significant DFS advantage for anastrozole versus tamoxifen in the oestrogen receptor-positive (ER+) progesterone receptor-negative (PR−) subgroup ($P < 0.0001$) [10,11]. However, following a reanalysis of the BIG 1–98 data by Dowsett *et al.*, no DFS advantage was evident for ER+ PR− patients in the letrozole arm [7,10,12].

A reanalysis of the BIG 1-98 subgroup data using a central pathological analysis determined that there was no difference between the subgroups with regard to efficacy [12,13]. Central versus local pathological assessment appears to have a bearing on the results of multicentre trials.

A comparative analysis of the ATAC and BIG 1-98 trials indicated that there was a trend towards lower HRs, particularly for breast cancer and overall survival, in the BIG 1-98 trial (Table 2). Heterogeneity testing, however, determined that there was no statistically significant difference between the trials [14].

The IES clinical trial demonstrated that switching from tamoxifen to exemestane significantly improved DFS ($P = 0.0001$) and overall survival ($P = 0.05$) at 5 years relative to continuing on tamoxifen [15]. A meta-analysis of three trials [ABCSG 8, ARNO 95, and Italian Tamoxifen Anastrozole (ITA)] demonstrated a 5-year survival advantage for switching from tamoxifen to anastrozole (HR 0.59; $P < 0.0001$) [16]. Separate analysis of the three studies, which had different designs and patient populations, demonstrated statistical significance favouring anastrozole for DFS ($P \leq 0.024$) across all trials. Overall survival, however, was significantly ($P = 0.026$) improved only in the ARNO 95 trial.

An analysis of subgroups in the IES trial clearly favoured exemestane over tamoxifen irrespective of node-positive or negative status, previous chemotherapy or prior tamoxifen therapy, ER-positive or unknown status (Fig. 1) [15].

Considering once again that across-trial comparisons are being used, the AIs do not appear to differ significantly with regard to the observed pattern of adverse events; all are associated to some degree with hot flushes, arthralgia, thromboembolic events, osteoporosis/fracture, gynaecological symptoms, hypercholesterolemia and cardiovascular events [17].

In conclusion, the AIs have proven superiority over tamoxifen and all AIs have a similar pattern of adverse events. Small differences in clinical outcomes between the AI studies appear to be primarily owing to differences

Table 1 Disease-free survival (DFS) outcomes for the aromatase inhibitor trials [5–9]

Trial	Study population	HR	95% CI	*P*
Upfront				
ATAC	ITT	0.87	0.78–0.97	0.01
	HR+	0.83	0.73–0.94	0.005
BIG 1-98	ITT	0.81	0.70–0.93	0.003
Switch				
IES	ITT	0.76	0.66–0.88	0.0001
	HR+/Unknown	0.75	0.65–0.87	0.0001
ARNO95/ABCSG-8 (EFS)	ITT	0.60	0.44–0.81	0.0009
Extended				
MA.17	ITT	0.57	0.43–0.75	0.0008

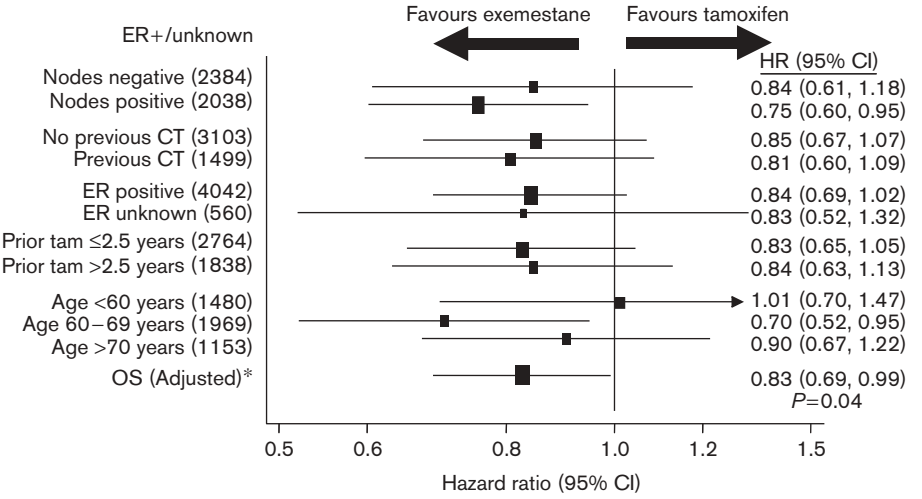
ARNO95, Arimidex–Nolvadex; ATAC, Arimidex, Tamoxifen, Alone or in Combination; BIG, Breast International Group; HR, hazard ratio; IES, Intergroup Exemestane Study; ITT, intention-to-treat.

Table 2 Comparative analysis of the Breast International Group (BIG) 1-98 and the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trials [14]

End point	Study	RR[a] (95% CI)	*P* value[c]	RD[b] (95% CI)	*P* value[c]
DFS	ATAC	0.83 (0.72–0.95)	0.890	−2.11 (−3.61–0.53)	0.618
	BIG 1–98	0.82 (0.70–0.95)		−1.62 (−2.83–−0.40)	
Distant relapse	ATAC	0.87 (0.70–1.06)	0.592	−0.78 (−1.92–0.34)	0.440
	BIG 1–98	0.76 (0.63–0.92)		−1.37 (−2.34–−0.41)	
OS	ATAC	0.98 (0.81–1.19)	0.370	−0.11 (−1.34–1.11)	0.488
	BIG 1–98	0.87 (0.71–1.06)		−0.64 (−1.56–0.26)	
BC survival	ATAC	1.00 (0.78–1.27)	0.065	−0.01 (−0.98–0.96)	0.093
	BIG 1–98	0.72 (0.57–0.92)		−1.07 (−1.86–−0.29	

BC, breast cancer; DFS, disease-free survival; OS, overall survival; RD, relative difference; RR, relative risk.
[a]Relative Risk: values <1 favor the AI, values >1 favor TAM.
[b]Risk Difference: values <0 favor the AI, values >0 favor TAM.
[c]Cochran's Q heterogeneity test.

Fig. 1



Subgroup analysis of overall survival for the Intergroup Exemestane Study [15]. CT, chemotherapy; *Adjusted for nodal status, chemotherapy and hormone replacement therapy.

in patient characteristics, different endpoint definitions, differing trial designs, the time points of randomization, differing analyses and central versus local pathological assessment. The results of the MA.27 trial, a head-to-head comparison of exemestane and anastrozole, and the Novartis-sponsored trial comparing letrozole with anastrozole will answer the question of whether there is differentiation between the nonsteroidal and steroidal AIs.

Conflicts of interest: none.

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