Aromatase inhibitors: their role in breast cancer

Third-generation aromatase inhibitors (AI) are already well established as the first-line treatment of advanced stage breast cancer. However, new data is emerging showing AIs to be a possible alternative to tamoxifen in early stage breast cancer. **Dr Andrew Wardley** reviews the role of AIs as a neoadjuvant, adjuvant or an extended adjuvant in this type of breast cancer.

DR ANDREW WARDLEY is a Consultant Medical Oncologist at the Cancer Research UK, Department of Medical Oncology, Christie Hospital, Manchester

The breast is an endocrine-sensitive organ; it undergoes significant changes in response to hormones during puberty, pregnancy and lactation. A significant proportion of breast cancers retain the intracellular apparatus for endocrine responsiveness, namely the oestrogen receptor (ER).

Tamoxifen, a selective oestrogen receptor modulator (SERM), has been the mainstay of endocrine therapy for around 30 years. When given to women with ER-positive (ER+) breast cancer for five years after surgery, it reduces the risk of recurrence by 41 per cent and risk of death by 34 per cent[1]. The partial agonist effects of tamoxifen can be beneficial (eg, reducing bone demineralisation) or it can be detrimental (eg, causing endometrial cancer and thromboembolism[2]). However, new data has shown aromatase inhibitors (AI) to be a potential alternative to tamoxifen. In postmenopausal women, the conversion of androgenic precursors to oestrogen by the aromatase enzyme occurs mainly in the adrenal glands, breast, fat and breast tumour itself. Third-generation AIs – letrozole and anastrozole (competitive non-steroidal inhibitors) and exemestane (an irreversibly steroidal inactivator) – inhibit oestrogen synthesis by 97–99 per cent[2,3]. This high degree of aromatase inhibition reduces circulating oestradiol to undetectable levels.

First-line for advanced breast cancer

Third-generation AIs are well established in the treatment of postmenopausal women with steroid hormone receptor-positive (SHR+) – also known as oestrogen receptor and/or progesterone positive – metastatic breast cancer. Trial data has shown them to initially demonstrate superiority to megestrol acetate (a progestin) as second-line therapy[4-6] and then tamoxifen as first-line therapy. The largest of these trials, involving over 900 women, showed letrozole to be superior to tamoxifen in terms of time to progression (9.4 *vs* six months, respectively), time to treatment failure (nine *vs* 5.7 months)), and overall objective response rate (32 per cent *vs* 21 per cent)[7]. A similar study with anastrozole showed it to have equal efficacy to tamoxifen but to be superior in terms of tolerability, fewer thromboembolic events and less vaginal bleeding[8]. More recently, a study of 382 patients with advanced breast cancer comparing exemestane with tamoxifen confirmed superiority of exemestane.

Adjuvant therapy with AIs

The success of AIs in advanced disease has led to several large trials comparing AIs with tamoxifen as adjuvant treatment following surgery in early

breast cancer. Different strategies have been adopted: immediate monotherapy for five years, and switching, sequential and extended treatment.

Immediate monotherapy

Two very large trials have addressed the question of immediate monotherapy (upfront) AI treatment for five years. The first of these was the ATAC trial. This involved a three-way prospective, double-blind randomisation of 9,366 postmenopausal women to five years anastrozole or tamoxifen, or anastrozole plus tamoxifen, following local therapy for invasive breast cancer and cytotoxic chemotherapy (if administered). At the first analysis, the combination arm was equivalent to tamoxifen and was closed. In this, and in subsequent analyses, anastrozole was superior to tamoxifen with respect to disease-free survival (DFS) especially in the ER+ population. Anastrozole consistently improved DFS in patients with ER+ breast cancer by 17 per cent, and the absolute difference in patients alive without recurrence improved from 1.6 per cent at three years to 2.5 per cent at five years[9]. There were also significant reductions in distant metastases and contralateral breast cancers; as yet, there is no evidence of survival benefit[9-11].

The second large trial was recently presented[12]. The Breast International Group (BIG) 1-98 trial, at a median follow-up of 25.8 months, showed an improvement of 19 per cent in DFS in the 4,003 women taking letrozole compared with the 4,007 women taking tamoxifen. The estimated three-year and five-year DFS differences were 1.5 per cent and 2.6 per cent, respectively. These results are very similar to original and mature results of the ATAC trial for anastrozole *vs* tamoxifen. Unlike ATAC, the most pronounced difference in the BIG 1-98 trial was in distant recurrence/metastasis: there was a 27 per cent reduction in the number of distant recurrences and metastases in the letrozole group compared with the tamoxifen group. Patients at highest risk appeared to derive more benefit from letrozole compared with tamoxifen; with a 29 per cent risk reduction compared with tamoxifen for those who had node-positive breast cancer[13].

Switching studies

An alternative strategy of switching endocrine therapy has been examined in two large datasets. The Intergroup Exemestane Study (IES) randomised 4,742 postmenopausal women with ER+ or unknown positive breast cancer, who had received between two and three years adjuvant tamoxifen, to either switch to exemestane or continue on tamoxifen to a total of five years[14]. The interim analysis showed that switching to exemestane resulted in a 32 per cent improvement in DFS at a median follow-up of 30.6 months. This translated into an estimated difference of 4.7 per cent in DFS three years after randomisation. The most recent data for IES shows switching to exemestane following two to three years of tamoxifen therapy significantly reduces the risk of dying[15]. A 40 per cent reduction in event-free survival (defined as time to relapse at any site or incidence of contralateral breast cancer) has recently been demonstrated for 1,618 chemotherapy-naïve patients switching to anastrozole after two-years compared with 1,606 remaining on tamoxifen in the combined ARNO 95 and ABCSG 8 trials[16].

It is not clear whether immediate AI or a sequential approach represents the best strategy. The BIG 1-98 is the only trial that involves a planned sequence (tamoxifen for two years followed by letrozole for three years, or letrozole for two years followed by tamoxifen for three years) in the same population that is randomised to monotherapy for five years. Sequence results from this trial are expected to report in 2007/8.

Extended adjuvant

The risk from ER+ breast cancer persists beyond five years, however, with approximately one-third of recurrences – and over half of all breast cancer deaths – occurring at this time[17].

Previously, there has been no proven therapy for women once they have completed five years of tamoxifen. This can leave many women feeling vulnerable, as they are no longer protected pharmacologically once tamoxifen ceases. The MA-17 trial, a phase III study of 5,187 postmenopausal women who had already completed approximately five years of adjuvant tamoxifen, has shown that letrozole (2.5mg) reduced risk of recurrence/death by 43 per cent compared with placebo after a median follow-up of 2.4 years[18]. The final analysis revealed a 39 per cent decrease in mortality for node-positive women randomised to letrozole, compared with those receiving placebo at a median follow-up of 2.5 years; it was the first data showing survival advantages for any AI[19].

New hope for successful breast-preserving surgery

The option of endocrine therapy before surgery offers the potential to avoid mastectomy. Two studies suggest AIs are better than tamoxifen in this area[20,21]. In the first, 324 postmenopausal women with large non-metastatic tumours were given letrozole or tamoxifen for four months prior to surgery[22]. Significantly more women taking letrozole went on to undergo breast-conserving surgery compared with tamoxifen (45 per cent *vs* 25 per cent). Following adjustment for tumour size, nodal involvement and age, the odds of having breast-conserving surgery rose by 70 per cent for women taking letrozole, halving the number of planned mastectomies[20]. An almost identical improvement in breast conservation was achieved with anastrozole in 124 women deemed to require mastectomy at initial assessment[21].

Adverse events

Both AIs and tamoxifen are well tolerated, with similar rates of adverse events overall. Side-effect profiles are best compared in the upfront treatment. There were more hot flushes and night sweats reported on tamoxifen. However, there were more complaints of joint (letrozole 20.3 per cent *vs* tamoxifen 12.3 per cent)[13] and musculoskeletal (anastrozole 27.8 per cent *vs* tamoxifen 21.3 per cent)[12] symptoms on AIs than tamoxifen. There are also increased rates of bone fractures on AI (42-60 per cent increase). This effect of increased oestrogen deprivation first became apparent in the ATAC trial and is equivalent to a bone fracture rate of 2.2 fractures per 100 patient years for AI compared with 1.5 fractures per 100 patient years on tamoxifen.

Tamoxifen stimulates endometrial growth, potentially leading to endometrial cancer. There is considerably less vaginal bleeding, lower endometrial biopsy rates and, most importantly, lower endometrial cancer rates on AI than tamoxifen. In the ATAC trial there was an almost fourfold increased rate of hysterectomy in patients on tamoxifen compared with anastrozole (5.1 per cent *vs* 1.3 per cent).

It might be expected that these drug classes would have different cardiovascular effects. Tamoxifen is known to be associated with venous thromboembolic events, whereas AIs are not. This cardiovascular side-effects profile was established in ATAC and confirmed in BIG 1-98. The BIG 1-98 trial systematically collected serum total cholesterol and enquired meticulously about cardiac events. There was a higher rate of hypercholesterolaemia for the patients receiving letrozole (43.5 per cent) than those receiving tamoxifen (19.1 per cent). Compared with tamoxifen, letrozole was associated with fewer thromboembolic events (1.5 per cent *vs* 3.5 per cent) though they had identical rates of cerebrovascular accidents/transient ischaemic attacks (one per cent *vs* one per cent) but more cardiac events (4.1 per cent *vs* 3.8 per cent). The observed excess of cardiac deaths, seen in BIG 1-98, might be explained by the absence of the

Table 1. Treamtent and adverse events

Adverse events	BIG1-98 (25.8 month analysis)			ATAC (33 month analysis)			ATAC (68 month analysis)		
	L	T		A	T		A	T	
Bone fractures	5.7%	4%	HR 1.42; p=0.0006	5.9%	3.7%	HR1.60	11%	7.7%	HR 1.43 p<0.0001
Vaginal bleeding	3.3%	6.6%		4.5%	8.2%				
Enormetrial biopsies	2.3%	9.1%							
Invsive endometrial	0.2%	0.5%	HR 0.40; p=0.087	0.1%	0.5%		0.2%	0.8%	HR 4.0 p=0.02
Cerebrovascular accidents/ transient ischaemic attacks				1.0%	2.1%				

A = anastrazole; L = letrozole; T = tamoxifen

Key points

- AIs are well established in the treatment of postmenopausal women with steroid ER+ metastatic breast cancer.
- Studies are underway to define the optimal sequence of AIs in adjuvant treatment: AI alone, tamoxifen followed by AI, or AI followed by tamoxifen.
- AIs are associated with reduced gynaecological, thromboembolic and vasomotor toxicity but increased rates of bone fractures and ischaemic heart disease.

potentially beneficial lipid-lowering effect of tamoxifen. There was no excess of either cardiac events or hypercholesterolaemia in the MA-17 trial comparing letrozole to placebo.

Conclusion

There have been two large trials demonstrating that the use of an AI as adjuvant endocrine therapy is superior to tamoxifen. Two large data sets show switching from tamoxifen to an AI after two to three years improves outcomes. The more mature of these shows an overall survival difference that may be significant. There remains uncertainty whether upfront use of an AI for five years or a sequential approach combining tamoxifen and an AI represents the optimal strategy. The results of the sequencing arms of BIG 1-98, as well as the TEAM trial, will hopefully answer this issue in due course. The individual patient's breast cancer risk – as well as competing health issues – should clearly be considered when prescribing adjuvant endocrine therapy. Patients at greater risk from breast cancer derive more benefit from more active treatments. To this end, there is apparently greater benefit for letrozole in patients who had node-positive breast cancer. In the future, we anticipate having better predictive tools for selecting individual treatment. A suggestion of different benefit rates in different cancers is suggested by subgroup analysis according to the progesterone receptor in ATAC[22] and human epidermal growth factor receptor status in primary medical therapy trials[23-24].

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