Has tamoxifen had its day?

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Anastrozole is being hailed by some as the new tamoxifen. But many researchers feel there is a great deal more we need to know before we consider casting aside the hormonal treatment that has served so many women so well.

Trialists of the aromatase inhibitor anastrozole are calling for the drug to replace tamoxifen as the preferred initial treatment for postmenopausal women with localised hormone-receptor-positive breast cancer. A five-year course of tamoxifen is the current standard treatment for this group of patients, which is prescribed to an estimated 500,000 women worldwide. The results of the ATAC trial (Arimidex, Tamoxifen, Alone or in Combination), published in the *Lancet* (365:60–62), showed women treated with anastrozole did better than those on tamoxifen in terms of disease-free survival, time to recurrence, distant metastases, and contralateral breast cancer.

The ATAC study is a double-blind randomised trial, comparing five years of anastrozole alone with tamoxifen alone, or in combination, as adjuvant therapy in 9366 postmenopausal women with localised breast cancer. The combination arm was closed early due to lack of efficacy, so the five-year results compare anastrozole alone against tamoxifen alone. After a median follow-up of 68 months, figures for disease-free survival showed 575 events for women treated with anastrozole compared with 651 for women on tamoxifen (hazard ratio 0.87, 95% CI 0.78–0.97, p=0.01). Time to recurrence was also better for the anastrozole group (402 vs 498, 0.79, 0.70–0.90, p=0.0005). If one looks only at the figures for women with hormone-receptor-positive breast cancer, the benefits are marginally greater: 0.83, 0.73–0.94, p=0.005, for disease-free survival and 0.74, 0.64–0.87, p=0.0002 for time to recurrence. The anastrozole group also did better in terms of reductions in contralateral breast cancers (all patients 35 vs 59, 42% reduction, 95% CI 12–62, p=0.01; hormone-receptor-positive patients 53%, 25–71, p=0.001).

Anthony Howell: anastrozole should replace tamoxifen as first-line treatment after surgery in hormone-receptive breast cancer

Anthony Howell, of the department of medical oncology at Christie Hospital, Manchester, who chaired the trial steering group, believes that these results indicate that anastrozole should replace tamoxifen as the standard treatment in hormone-receptive breast cancer. "On the basis of the ATAC data, we feel it is appropriate to begin adjuvant therapy with anastrozole as first-line treatment after surgery for breast cancer in patients with hormone-receptor-positive tumours," he said. "The reason is that if you start someone on tamoxifen during the first 2.5 years there are quite a lot of relapses which are prevented by anastrozole. When a patient gets a relapse, that usually ends in further systemic disease and,

Henning Mouridsen: tamoxifen is treatment of choice for first two years, unless there are thromboembolic concerns

Andrea Decensi is testing a combination similar to the ATAC combined arm, but with a lower dose of tamoxifen

I am afraid, death. Thus, preventing lapses at all costs is very important."

Overall survival

The study has not, so far, shown any difference in overall survival (hazard ratio 0.97, 95% CI 0.85–1.12, p=0.7). However, the trial group argues that this is to be expected since the trial population had relatively good prognoses: 61% of patients were lymph node negative and 64% had tumours of 2 cm or smaller. They point out that trials of tamoxifen versus placebo took at least seven years to show a significant survival advantage, and argue that the reductions in recurrence and distant recurrence associated with anastrozole strongly suggest that a reduction in deaths from breast cancer will eventually be seen.

"We are already seeing fewer metastases and this trend is going to get stronger," said Howell.

But other researchers believe the results of the study do not provide sufficient evidence to warrant abandoning tamoxifen as the first-line treatment for this group of women. Their reservations concern the lack of evidence about the long-term effects of anastrozole, and the fact that we have no way of predicting which women are likely to benefit from it. There are also concerns about the cost and questions about length of treatment.

Henning Mouridsen, professor of oncology at Rigshopitalet, Copenhagen, has recently reviewed the role of aromatase inhibitors in the treatment of postmenopausal women with early breast cancer (*EJC*, in press). He considers that while aromatase inhibitors have an important role in adjuvant treatment, their long-term superiority over tamoxifen remains uncertain. He believes that the optimal treatment approach still needs to be defined, and argues that sequencing tamoxifen with an aromatase inhibitor may prove superior to non-sequenced therapy with an aromatase inhibitor.

Mouridsen's view is that tamoxifen should remain the treatment of choice for the first two years, with a possible switch to an aromatase inhibitor at that point. "The key scientific question yet to be answered in randomised trials is whether any superiority is associated with the upfront or the sequential approach," he said.

He points out that at the international conference on primary therapy of early breast cancer in St Gallen, Switzerland, in January, the consensus panel was in favour of maintaining tamoxifen as the standard treatment for postmenopausal women with early breast cancer.

"Tamoxifen is still the treatment of choice for the first two years unless there are thromboembolic concerns," he said.

Andrea Decensi, director of the chemopreventive division of the European Institute of Oncology, Milan, and director of the division of medical and preventive oncology at Galliera Hospital, Genoa, believes the increased risk of endometrial cancer associated with tamoxifen could be addressed by reducing the standard dose. Preliminary results of a cooperative Italian Norwegian study headed by Decensi show that reducing the amount of tamoxifen by three quarters is still effective in reducing the incidence of breast cancer.

He believes the best answer may lie in combining tamoxifen with anastrozole, and says that the problems with the combination arm of the ATAC trial might have been due to the dosage: "I

"Fewer recurrences and metastases suggest anastrozole may eventually show better survival"

"Tamoxifen may still be effective when used at one-quarter of the standard dose"

think 20 mg per day of tamoxifen might have been too high in combination with anastrozole." He is currently studying the effects of a combined Arimidex and tamoxifen regimen using a lower dose of tamoxifen.

Martine Piccart, head of medical oncology at the Jules Bordet Institute, Brussels, is coordinator of the TRANSBIG trial into genetic targeting of breast cancer treatment. She believes the problem lies less in the choice of drug than the choice of patient. "We are entering an era of individualised treatment and at the same time we are lacking strong predictive tools for judging which women will do best on which treatments," she said.

She is not convinced that five years of endocrine therapy is enough for women at high risk. "We have five very positive trials and my personal view is that most women who I see in my clinic should be considered candidates for an aromatase inhibitor. But that is not to say that all women should be given anastrozole from the beginning and for five years. Things are more complex than that. The ATAC trial is certainly the longest follow-up but the benefits are still relatively small in percentage terms.

"We now have two trials showing that two years of tamoxifen and then an aromatase inhibitor is effective. I am very tempted to go for tamoxifen and then an aromatase inhibitor in women whose tumours express high levels of estrogen and progesterone receptors."

Side effects

The ATAC trial found that, compared with tamoxifen, treatment with anastrozole was associated with significant reductions in the incidence of endometrial cancer, thromboembolic events, ischaemic cerebrovascular events, vaginal bleeding, hot flushes and vaginal discharges. However, there were more fractures and more arthralgia among women on anastrozole than among the group on tamoxifen.

Fracture rates per 1,000 woman years were 22.6 for anastrozole and 15.6 for tamoxifen. The risk ratios for all the prespecified adverse events were similar, says the trial group, to results in two analyses conducted earlier in the trial (*Lancet* 2002, 359:2131–39; *Cancer* 2003, 98:1802–10), suggesting that that the safety profile of anastrozole remains unchanged during the five-year treatment period. "No new safety concerns emerged," they said.

Howell points particularly to the drop in the incidence of endometrial cancer, from 0.8% of women on tamoxifen to 0.2% of women on anastrozole. This, he argues, has a wider significance on women's quality of life because of the spin-off effect on cutting down the number of hysterectomies – many of which may be unnecessary. "Gynaecologists are rightly worried that any form of prob-

Martine Piccart: we need ways to predict who will respond best to which drug, used alone, in sequence or in combination

lem in the uterus may lead to endometrial cancer on tamoxifen and I suspect this leads to the excess of hysterectomies." he said. The results show 5.1% of women on tamoxifen had hysterectomies compared to 1.3% of women on anastrozole." The problem of increased fractures, he argues, can be managed by bisphosphonates.

The ATAC group also point out that withdrawals due to drug-related serious adverse events were significantly less common with anastrozole (4.7% vs 9.0%). "Since almost all patients have completed their scheduled five years of therapy, the safety and tolerability of therapy can be deemed final," the study concluded.

Class effect?

The ATAC study, says Howell, is the largest study ever done in early breast cancer, and its results have been treated as reliable as far as anastrozole are concerned. But how much does it tell us about the effects of aromatase inhibitors as a class of drugs?

The trial group stipulate that the results are only applicable to anastrozole "since it is unknown how differences between the aromatase inhibitors affect their clinical usefulness." However, Howell believes that there may be a class effect, though treatment decisions must be made on the basis of best evidence.

"As a clinician you treat somebody with the drug with which you have most experience. At the moment we have most evidence on anastrozole. But in five years it may be letrozole.

"All the aromatase inhibitors are associated with fewer deep vein thromboses and a good gynaecological profile. They are all associated with osteoporosis and increased joint aches in some women," he said. He added, however, that "exemestane and letrozole are associated with increased cardiac deaths which are not seen on anastrozole."

Mouridsen also feels it is too early to say whether there is a class effect for aromatase inhibitors. He argues that, while there clearly are differences between their mode of action and potency, we lack data that can relate these differences to clinical activity. He believes that while the evidence for aromatase inhibitors grows increasingly strong, many questions remain about the most effective use of tamoxifen and aromatase inhibitors in adjuvant treatment. "These questions relate primarily to the optimal single agent or sequence, duration of treatment and selection of individual patients," he said.

The ATAC trial seems to point to a growing role for aromatase inhibitors in the treatment of postmenopausal women with early breast cancer, in particular in patients at cardiovascular risk.

The trialists argue that the higher rates of recurrence, especially in years 1–3, and the increased numbers of adverse events and treatment withdrawals associated with tamoxifen, "lend support to the approach of offering the most effective and tolerated therapy at the earliest opportunity." Many other seasoned researchers, however, urge caution before ditching tamoxifen, which has served hundreds of thousands of women so well over the last three decades.

More time is needed, they argue, to evaluate the impact on survival and the long-term toxicity of anastrozole. And further research is needed to establish whether anastrozole is really more effective when prescribed alone rather than in combination or sequenced with tamoxifen, and to identify which women are most likely to benefit and the optimum length of treatment duration.

"Fears of endometrial cancer on tamoxifen may lead to many unnecessary hysterectomies"

Decensi, who is involved in a separate study on tamoxifen and anastrozole, is concerned about the lack of data on the potential long-term toxicity of anastrozole. "This is a good study and it's clear the new drug has potent advantages. But we have to be very prudent. Toxicity may become apparent after several years," he said. The fact that fractures and arthralgia are higher among women on anastrozole is also a concern for clinical practice, he added.

Decensi also points out that cost is an issue here, as anastrozole is much more expensive than tamoxifen. He believes the new drug can only be justified as a first-line treatment in women who are at cardiovascular risk. Piccart concurs with Decensi that the side-effect benefits of anastrozole over tamoxifen are relatively small in percentage terms.