

New treatment strategies for women with early-stage breast cancer - should we draw a line under the tamoxifen era?

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International specialists discuss the evidence driving clinical practice

by Stephen Pinn

Introduction

Until recently, a five-year period of endocrine treatment with tamoxifen was widely acknowledged as being the gold standard, adjuvant therapy for postmenopausal women with early breast cancer (EBC). Despite the clear benefits of tamoxifen, however, many patients still develop recurrent disease. Furthermore, patients on tamoxifen may experience serious side effects - such as thromboembolic/cerebrovascular events and endometrial cancer.

Recent clinical data suggest that the new generation of aromatase inhibitors (AIs) provide more effective protection against breast cancer recurring than tamoxifen - while at the same time reducing the risk of complications.

A group of 15 internationally renowned breast cancer specialists (oncologists, surgeons and gynaecologists) is so concerned that women with EBC are continuing to receive sub-optimal endocrine treatment that they met to discuss the prevailing evidence on the use of AIs as adjuvant treatment.

Meeting in the UK (April 25-26, 2008), members of this forum first considered why postmenopausal hormone receptor-positive women with EBC should be treated with endocrine therapy in the first place:

- to prevent recurrence
- to prolong survival
- to minimise life-threatening side-effects
- to maintain quality of life

The American Society of Clinical Oncology (ASCO) and the National Institute for Health and Clinical Excellence (NICE) both signal that AIs should be playing an essential part of treatment strategies in this vulnerable cohort of women. However, clear guidance as to the timing of AI initiation remains somewhat vague. While there is a steady take-up of AIs as the endocrine treatment of preference, there is still a reluctance to commit to AIs up-front in some countries.

What do the clinical trials tell us?

Many oncologists have been persuaded that 2-3 years of tamoxifen before switching to an AI provides the best available endocrine strategy - certainly better than persisting with tamoxifen for 5 years. But have they been seduced by switching trials such as the IES (Intergroup Exemestane Study)? In the IES,

4,724 postmenopausal women with EBC who were disease-free after 2-3 years on tamoxifen were randomly assigned to continue with tamoxifen for the remainder of a 5-year period of endocrine therapy or switched to an AI (exemestane).

After a median follow-up of 55.7 months, there was a significant benefit in terms of disease-free survival favouring the AI (HR 0.76, $p=0.0001$) - an absolute difference compared with tamoxifen of 3.3% (i). In addition, a "modest" improvement in overall survival (OS) was seen. However, what is not widely understood is that the observed benefit in OS may be due to an effect on non-breast cancer deaths rather than breast cancer-related events.

To date, the upfront trials ATAC (Arimidex, Tamoxifen, Alone or in Combination) and BIG1-98, have not demonstrated an OS benefit for AI therapy, and clinicians continue to be cautious about up-front AI therapy (ii, iii). However, the specialists who took part in the UK forum recognise that there are competing causes of mortality that increase with age which decrease the likelihood of being able to easily demonstrate a better survival outcome with AIs. "In a sense," said Dr Jack Cuzick (Wolfson Institute of Preventive Medicine, London, UK), "it means that these women are not dying from breast cancer, but from other causes. We must make sure that oncologists appreciate the significance of the difference in recurrence with an AI. It is totally unrealistic to expect a decrease in OS."

However, in the ATAC trial, fewer deaths after recurrence were seen on anastrozole compared to tamoxifen. Based on the outcome of studies comparing tamoxifen to placebo (iv), Dr Chlebowski suggested "follow-up exceeding 10 years may be needed before an overall survival benefit could be anticipated to emerge".

More recently, 100-month data from the ATAC trial have revealed that the benefits of managing hormone-sensitive EBC with an up-front AI (anastrozole) are maintained well beyond the conventional 5-year course of treatment (ii). Following initial surgery to remove their tumour, 9,366 postmenopausal women with invasive EBC were randomised to 5 years of adjuvant hormonal therapy, receiving either anastrozole, tamoxifen or a combination of both.

Intriguingly, the 100-month data from ATAC suggest that the "carry over" benefit favouring anastrozole over tamoxifen actually increases with time. At 5 years of follow-up, time to recurrence in hormone receptor-positive patients showed an absolute advantage of 2.8% when compared with tamoxifen. This increased to 4.8% after 9 years, representing the first demonstration of a strong carry-over effect for an AI over and above tamoxifen in the years following completion of adjuvant hormonal therapy (ii).

How should data from the trials be interpreted? Explaining the carry-over effect

Those taking part in the UK forum acknowledge that the absolute benefit of 4.8% seen in the 100-month data from ATAC with an AI might seem small. However, it compares favourably with other clinical data that have already had a widespread impact on clinical practice (e.g. an absolute benefit of 2.7% reduction in recurrence for 5 years vs 2 years of tamoxifen) (v).

They concede that the "carry-over" effect may be a difficult concept to understand. The term "carry over" may even be confusing clinicians, and might be better described as a "cure" effect. Thus, if malignant cells are killed during endocrine therapy, future recurrences are prevented.

Dr Cuzick says that the carry-over effect should not be so mystical. "If you eradicate micro-metastases in just a small proportion of patients, it's an effect that lasts forever. In those patients, this is a cure - and it establishes the case for treating with an AI in the first few years to create a benefit later on."

Data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) show that while the carry-over benefit with tamoxifen only extends to 10 years of follow-up (v), there is every expectation that the additional benefit of AI therapy will continue for 20 years and possibly longer.

Even if clinicians accept the evidence for giving up-front AIs, cost may be an issue. Members of the forum argue, however, that the impact of recurrence is too great a price to pay for not choosing a therapy that has been shown to significantly reduce that risk. They emphasise that the psychological impact of recurrence cannot be overestimated in terms of anxiety and stress and a negative impact on overall quality of life.

Finally, it has been reported that although there is evidence that endocrine therapy of longer duration than 5 years is worthwhile, there are no data on optimal duration of AI therapy. Therefore, careful selection of patients and detailing the risk profile of individual patients will be important in justifying longer duration of AI therapy. There may well be a benefit in terms of recurrence, but whether or not long-term toxicities will compromise extended duration of the therapy is not known - and may never be known.

The impact of non-breast cancer deaths and other side effects with tamoxifen and AIs - is this an issue?

In the management of women with EBC, clinicians do not always think about the impact that their prescribed therapies are having on other aspects of their patients' health and well-being, or on other potential causes of mortality. In terms of therapeutic intervention, their decisions tend to focus largely upon what can be done to minimise the risk of recurrence.

Members of the forum were anxious, however, to stress that as adjuvant endocrine therapy does not offer all women a cure for breast cancer, it is vital that those women experience an optimal quality of life during the course of their remaining years.

With this in mind, the risk:benefit profile of AIs is an important issue. Are clinicians being deterred from prescribing AIs because they perceive that the side effects of therapy outweigh the proven advantages in extending time to recurrence?

Professor Rowan Chlebowski (University College of Medicine, Los Angeles, US) commented that the side-effects of endocrine treatment must be put into perspective. "The scarcity of adverse events is more striking than any potential safety differences between tamoxifen and AIs," he said. "We can be too negative about side-effects. We must convince patients of the benefits of persisting with therapy through years 3, 4 and 5 - not just year 1."

It was pointed out that much has been made of the link between AIs and an increased risk of musculo-skeletal problems - but that while these may be troublesome, they are not life-threatening, and can be treated. Indeed, when the risks associated with AIs (e.g. bone fractures and arthralgias) are compared with that of tamoxifen (e.g. life-threatening endometrial cancer, strokes, pulmonary embolism, urinary sarcomas) few oncologists would think twice about prescribing an AI.

Meanwhile, the ATAC 100-month data also indicate that the excess fracture risk associated with active anastrozole therapy - a continuing concern for physicians considering AI therapy in this setting - completely disappears within a matter of months of stopping treatment (ii).

Promoting adherence to endocrine treatment in EBC

Even if clinicians are persuaded by the powerful arguments in favour of up-front AIs, there may be a problem of convincing women with EBC that they need to persist with these new agents. Professor Peyman Hadji (University of Philipps-Marburg, Germany) highlighted the importance of adhering to endocrine therapy - at least for the 5-year period currently recommended.

There is no question, he said, that AIs offer greater benefit than tamoxifen in terms of risk of recurrence - but how to keep patients on AIs when they perceive that the side-effects of therapy outweigh those benefits?

It has been reported that compliance in adjuvant endocrine therapy for early breast cancer is sub-optimal almost from the outset - 87% still on therapy at 1 year, and as low as 50% at 4 years (vi). From a more recent German database, it is clear that failure to comply extends across all currently available endocrine therapies in this setting - anastrozole, exemestane, letrozole and tamoxifen - 30-38% at 3 months, rising to a 42-50% rate of non-compliance at 15-18 months (vii).

Professor Hadji says that a significant proportion of patients do not perceive an improvement in their symptoms or the likelihood of a cure. Patients will not experience an immediate benefit since there are no acute symptoms from which AIs give relief - but AIs do reduce the risk of recurrence and distant metastases. Furthermore, a significant percentage of patients who say they are compliant, are not. As with clinicians, they may have difficulties in accepting that the side effects associated with AIs pale into insignificance when compared with the potential benefits.

"We must strike a balance," he says, "between telling patients about the potential for side effects from AI therapy - none of which are life-threatening and most of which can be treated successfully, and the need to warn women that recurrence and its consequences are a constant risk of non-adherence."

"It underlines," says Professor Hadji, "the importance of communicating with patients from the outset - involving women with EBC in the choice of endocrine therapy, and increasing the intensity of consultations in the first 3-6 months following diagnosis, to ensure patients understand the importance and value of their treatment and the potential side effects."

Conclusion

The members of this international forum of breast cancer specialists are planning to publish proceedings from their discussion later in 2008. Professor Chlebowski concluded: "We have to convince clinicians that an up-front strategy with AIs will pay dividends - and we have to convince patients that they have to take their treatment for the duration of prescribed therapy. If cost were not an issue, there would be no argument against giving an AI up-front."

He asked: "Are we being totally honest with our patients? Do they really have any conception that a diagnosis of recurrence or contralateral breast cancer - particularly evidence of distant metastases - is a death sentence, and that the prospect of having to return to chemotherapy and/or radiotherapy would be devastating?"

References

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The UK forum was chaired by Professor Rowan Chlebowski (USA). The other participants were: Jack Cuzick (UK), Peyman Hadji (Germany), Shinzaburo Noguchi (Japan), Sunil Verma (Canada), Stephen Chia (Canada), Andre Robidoux (Canada), Nicholai Maass (Germany), Ingo Bauerfeind (Germany), Bruno Cutuli (France), Aman Buzdar (USA), Rick Linforth (UK)

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