Aromatase inhibitors in the hormonal treatment of breast cancer

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Aromatase inhibitors are established as first line palliative therapy in metastatic breast cancer but as yet are only considered appropriate adjuvant hormonal therapy for early breast cancer in certain patients.

For 30 years, tamoxifen has been the initial hormonal treatment of choice for women with early or advanced hormone-sensitive breast cancer. Over the last five years, the specific aromatase inhibitors have challenged that role in postmenopausal women.

What are specific aromatase inhibitors?

In postmenopausal women, the major source of circulating oestrogens is the conversion of precursors (mainly androstanedione) by an aromatase in fat, liver and muscle tissues. Inhibiting this enzyme will reduce circulating oestrogen levels by about 95% and cause reduced activity of hormone-sensitive breast cancers.

The three commercially available specific aromatase inhibitors are:

- anastrozole (Arimidex) – nonsteroidal, daily dose 1 mg
- letrozole (Femara) – nonsteroidal, daily dose 2.5 mg
- exemestane (Aromasin) – steroidal, daily dose 25 mg.

These third generation aromatase inhibitors supercede the parenteral second generation inhibitors and totally replace aminoglutethimide, the first available aromatase inhibitor, for the treatment of breast cancer. Aminoglutethimide is much less effective than the selective inhibitors because it inhibits several enzymes and has many side effects. None of these aromatase inhibitors have a role in treating breast cancer in women with functioning ovaries.

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When are they used?

Palliative therapy for metastatic breast cancer

Anastrozole, letrozole and exemestane were investigated initially for the management of metastatic hormone-sensitive breast cancer in postmenopausal women. They are more active than tamoxifen and/or progestogens in this setting, and are indicated as first line agents for metastatic disease, although the PBS listing for exemestane requires prior use of tamoxifen. While there are few data comparing anastrozole and letrozole, there are some early figures suggesting that a few cancers that become resistant to these nonsteroidal medications may have a second response to the steroidal medication exemestane.

Adjuvant treatment of early breast cancer

The initial results of four large trials in hormone-sensitive early breast cancer have recently become available.[1-4] In each study, the aromatase inhibitor was compared to tamoxifen or to placebo following standard tamoxifen therapy. These studies show aromatase inhibitors are more effective than tamoxifen in reducing the rate of breast cancer recurrence. However, these results are limited because the analyses were performed after relatively

Table. Occurrence of predefined adverse events in the ATAC trial[1]

Adverse event	Anastrozole (n=3092)	Tamoxifen (n=3094)	Significant (p<0.05)
Hot flushes	35.7%	40.9%	Y*
Nausea and vomiting	12.7%	12.4%	N
Fatigue/tiredness	18.6%	17.6%	N
Mood disturbance	19.3%	17.9%	N
Musculoskeletal symptoms	35.6%	29.4%	Y
Vaginal bleeding	5.4%	10.2%	Y*
Vaginal discharge	3.5%	13.2%	Y*
Endometrial cancer	0.2%	0.8%	Y*
Fractures	11.0%	7.7%	Y
Ischaemic cardiovascular disease	4.1%	3.4%	N
Ischaemic cerebrovascular disease	2.0%	2.8%	Y*
Any venous thromboembolic event	2.8%	4.5%	Y*
Deep venous thrombosis	1.6%	2.4%	Y*

*Favours anastrozole

short periods of treatment and follow up. The large numbers of women in each study (3000 to 9000 women) meant that predefined endpoints were reached early, when statistically rather than clinically significant results were achieved.

Does this mean that tamoxifen is no longer the gold standard? For premenopausal women, tamoxifen remains the treatment of choice. For postmenopausal women, the decision is more complex. The side effect profile of aromatase inhibitors is somewhat different to that of tamoxifen (see below and the Table). In particular, osteoporosis may turn out to be a significant issue. Also, aromatase inhibitors are significantly more expensive than tamoxifen. Only anastrozole is currently reimbursed by the PBS in the adjuvant setting, and only where tamoxifen is contraindicated or not tolerated. The most common toxicity favouring an aromatase inhibitor over tamoxifen is a patient's significant risk of venous thrombosis.

Studies are in progress looking at switching hormonal therapy from tamoxifen to aromatase inhibition after two to three years of initial tamoxifen therapy. Aromatase inhibitors are also being investigated as a chemoprevention agent for healthy women at increased risk of getting breast cancer.

At present, given the extra cost and uncertain long term side effects of aromatase inhibitors, the decision to prescribe an aromatase inhibitor in the adjuvant setting must be made in the light of an individual woman's risk of tumour recurrence balanced against potential side effects and her personal wishes. This recommendation will undoubtedly be revised in the light of additional information in the future.

What are the side effects?

The main side effects of aromatase inhibitors are those probably related to low levels of circulating oestrogens, such as hot flushes, mood disturbance, musculoskeletal symptoms, osteoporosis and bone fractures. The Table shows a comparison of the side effects of aromatase inhibitors and tamoxifen as demonstrated in the blinded ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.[1] More data about long term effects, particularly on bone and cardiovascular disease, are important, especially in the adjuvant setting. There are no local guidelines at present for the screening and management of osteoporosis in patients on aromatase inhibitors.

Conclusion

We are in a period of transition in the hormonal therapy of both early and advanced breast cancer. It is important that treatment decisions are guided by the best available clinical trials information to achieve the best outcomes for women with this cancer. MT

References

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