



Hormone HELP

» **Breast cancer** | By Lynda Wharton

Tamoxifen is a drug commonly used in managing specific stages of some breast cancers, but it does attract controversy. Lynda Wharton examines the research to explain why it is effective, and looks at the possible and common side-effects

{ This year, more than 2,300 New Zealand women will learn that they have breast cancer. While still in shock from their diagnosis, they will be faced with numerous treatment decisions. One of the most perplexing and complicated of these will be the question of long-term pharmaceutical intervention, in the hope of preventing a recurrence of the disease.

A 'yes' decision means that for the next two to five years, they will take a daily dose of one of several potent drugs that offer a complex combination of risks and hoped-for benefits. That drug of choice will belong to one of two categories: Selective Estrogen Receptor Modulators (SERMS), the most common of which is Tamoxifen;

or Aromatase Inhibitors (AIs), including the commonly prescribed Arimidex.

Approximately 70% of all breast cancers are sensitive to the stimulatory effects of oestrogen, and are known as oestrogen receptor positive cancers (ER positive). Both categories of drugs above are designed to reduce the chance of relapse by decreasing the stimulatory effect of oestrogen on breast tissue, but they achieve this in quite different ways.

SERMS such as tamoxifen and raloxifene inhibit the ability of oestrogen to stimulate hormone-sensitive cancers by binding to oestrogen-sensitive receptors in the breast. These receptors function as cellular 'keyholes', shaped to take an oestrogen 'key'. Ordinarily, they are filled by oestrogen molecules produced naturally by the body, or by synthetic oestrogens introduced through hormone replacement therapy or the oral contraceptive pill. SERMS are shaped to fill these keyholes, preventing oestrogen from docking with the cellular receptors, thereby blocking its growth-stimulating effects.

Unfortunately, the anti-oestrogenic effect of SERMS is not limited to breast cells, and many of the common side-effects of use are a result of oestrogen-blocking in other tissues. These may include hot flushes, vaginal discharge and dryness, depression and confusion, bladder irritation and weight gain.

While these symptoms do affect quality of life, of more concern are the well-documented, potentially life-threatening risks associated with the use of SERMS. Tamoxifen irritates the linings of the veins, leading to inflammation and an increased risk of blood clots. In fact, both the oral contraceptive pill and Tamoxifen increase blood clot risk by anywhere from two to seven times higher than normal, depending on other risk factors.

We also need to consider that SERMS are bizarrely schizophrenic drugs. In some parts of the body, they act as an oestrogen blocker, but in others, they are a potent oestrogen enhancer. Working as an oestrogenic stimulant on the lining of the uterus – the endometrium – Tamoxifen increases the risk of endometrial cancer risk by up to 700%. In almost 70% of cases, these growths are serious, difficult-to-treat, high-grade tumours. And they are only found in 24% of other endometrial cancer sufferers who are not using Tamoxifen.

So, Tamoxifen is a controversial drug; any of its critics point to the exquisite irony of using a known carcinogen to beat cancer. In 1996, the World Health Organisation added Tamoxifen to its list of known human carcinogens, pointing to the six-fold increase in the chance of liver cancer after only two years of use. In the same year, the International Agency for Research on Cancer concluded that "there is sufficient

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evidence to regard Tamoxifen as a human carcinogen that increases a woman's risk of developing cancer of the endometrium".

This all means that every woman considering Tamoxifen should be asking some serious questions and weighing up her own risk/benefit profile. The success statistics are all there, with her risk of recurrence reduced by half, along with a significant decrease in the likelihood of cancer occurring in the opposite breast (contra lateral cancer).

However, there are a few points every such woman needs to understand. Firstly, if she has an ER positive cancer that has not spread into any lymph nodes, the chance of the extra 10 years offered to her by Tamoxifen will actually only be around 5% – up from 73.3% to 78.9%. If her cancer has spread into her lymph nodes, the increased survival period attributed to Tamoxifen will be about 10% – up from 50.1 to 61.4%.

The thing is, many Tamoxifen studies have shown that, while there is a decrease in the recurrence of breast cancer or the development of cancer in the opposite breast, the actual decrease in mortality as a result of using Tamoxifen is disappointingly low. A large meta-analysis of 55 trials, involving 37,000 women with ER positive tumours, showed that while five years of Tamoxifen use reduced the breast cancer recurrence rate by 47%, the actual improvement in 10-year survival rates was a less than impressive 11%.

So, when a woman is told that Tamoxifen will reduce her risk of a recurrence by 50%, she needs to ask: "50% of what? What is MY likelihood of a recurrence without Tamoxifen?". It is also worth noting that the use of Tamoxifen after chemotherapy has been shown to offer little or no survival benefit, and this is the case in both pre- and post-menopausal women.

And when balancing risks versus benefits, most studies have shown that post-menopausal women with ER positive cancers are likely to fall into the group for

whom the benefits outweigh the risks. For pre-menopausal women, though, the decision is much harder, with the potential benefits likely to be small. In general, women whose cancer has spread into their lymph nodes are likely to receive more benefit from Tamoxifen than women with lymph node-negative cancers.

Aromitase Inhibitors are a relative newcomer to the pharmaceutical cancer arsenal, with Arimidex being one of the most widely prescribed AIs in New Zealand. Like Tamoxifen, this drug reduces the oestrogenic stimulation to breast cells, but it achieves this by very different means.

Unlike SERMs, which are prescribed for women of all ages, AIs are prescribed only for post-menopausal women suffering from both early and advanced ER positive breast cancers. The idea is that, after menopause, the ovaries produce little oestrogen. Instead, much of this hormone in the body comes from the conversion in the fat cells of adrenal hormones into oestrogen. This requires an enzyme called aromatase, and the purpose of AIs is to directly inhibit this process.

However, tinkering with female hormones always produces unwanted spin-off effects. By lowering systemic oestrogen levels, AIs can cause hot flushes, night sweats, vaginal dryness, and hair and skin thinning. Joint pain and weakness are also an especially debilitating symptom for around 20% of AI users.

One of the most concerning effects of AIs, though, is their negative effect on bone density. A woman using Arimidex for five years can lose around 7% of her bone density. In women who already have a lowered density at the onset of treatment, such a loss can lead to osteoporosis. And limiting the duration of the drug use is of no benefit either, as the greatest loss occurs in the first two years of use.

Along with this side-effect comes a 40% increase in the risk of fractures in women taking an AI drug. Therefore, it is strongly

advisable to have a bone density test carried out before commencing AI use, and to repeat it every year whilst taking the drug. It is also recommended to use a calcium and vitamin D supplement for the duration of the drug course. Essentially, as AIs are a new class of medication, it will be many years before the long-term consequences of their use are understood.

Given all this, it's hardly surprising that much attention is currently being paid to determining the relative benefits of AIs over the more traditional SERMs. A flurry of recent studies have tended to indicate that AIs have the edge over their predecessors when it comes to preventing cancer recurrence in the five years after diagnosis... bearing in mind that only post-menopausal women can use AIs, so those who are pre-menopausal have no choice between the two approaches.

The so-called ATAC study is one of the world's largest and longest running research projects investigating women with breast cancer. Results to date show that Arimidex can help more women live cancer-free for longer, compared to Tamoxifen; and it is 24% more effective in preventing long-term cancer recurrence. There is, however, no evidence that this translates into reduced mortality rates resulting from AI use rather than SERM use. Other studies are also suggesting that women who start their treatment on Tamoxifen, but swap to an AI after a year or two, still show an increased benefit over those using Tamoxifen alone.

In the next issue, part two of this story looks at drug-free self-help options for breast cancer patients. ◀◀

"Many disparate effects of Tamoxifen in different tissues produce a complex mix of benefits and risks requiring highly individualised assessment of the overall benefits for every woman considering its use." *Journal of the National Cancer Institute* 1999