Prescribing guidelines:

Medications to reduce the risk of familial breast cancer

Clinical Oncology Society of Australia

Background

This document provides information about prescribing selective oestrogen receptor modulators (SERM) to cancer-unaffected women for breast cancer prevention purposes. These guidelines were prepared by the COSA Familial Cancer Group in response to a need for further information for those working in the field. A discussion of other strategies available for breast cancer risk reduction is beyond the scope of this document.

Medications to reduce the risk of familial breast cancer

There are a number of medications available that reduce the risk of breast cancer. The two most commonly prescribed drugs, tamoxifen and raloxifene, are both selective oestrogen receptor modulators (SERM). Although these medications are approved by the TGA, none are currently listed on the PBS for breast cancer prevention purposes (they are listed for other indications).

A number of large studies have shown that SERM are effective in preventing oestrogen receptor positive (ER+) breast cancer, which is the most common type of breast cancer. SERM are **not** effective in preventing oestrogen receptor negative (ER-) breast cancer.

How do SERMs reduce the risk of developing breast cancer?
Oestrogen binds to and activates the oestrogen receptor in ER+ breast cancer cells. A SERM blocks an ER+ breast cancer cell's growth by binding to the oestrogen receptor. This prevents oestrogen from binding, preventing oestrogen from "assisting" the growth of cancer cells. In other words, a SERM acts like a key broken off in the lock that prevents another key from being inserted.

Who can benefit from using SERM?
Up to 5% of women have a moderate or high risk of developing breast cancer based on their family history. These women may benefit from using a breast cancer risk-reducing medication.

What are the benefits of SERM?

- A daily dose of a SERM taken for five years reduces the risk of ER+ invasive and non-invasive (i.e. DCIS) breast cancer by around 40% - in other words, they reduce the risk by more than a third.
- The benefit of tamoxifen lasts for at least 8 years after completing the 5 years of treatment.
- It is not known how long the benefit of raloxifene lasts after completing 5 years of treatment.
- Both tamoxifen and raloxifene can help prevent osteoporosis.
    - In post-menopausal women, raloxifene slows down bone turnover and increases bone density at the lumbar spine and femoral neck. Raloxifene reduces the incidence of vertebral fractures by 40-50%, but has not been shown to decrease the incidence of non-vertebral fractures
    - In premenopausal women tamoxifen causes bone loss but at low levels that do not seem to present a clinical problem
    - In post-menopausal women tamoxifen slows down loss and may prevent osteoporosis.

Tamoxifen

Tamoxifen is suitable for pre and post-menopausal women.

What effect does Tamoxifen have on the chance of developing breast cancer?

- Tamoxifen removes about 40% of a women's risk of breast cancer.
- If the chance of developing breast cancer in the next 5 years is 1 in 10 (10% risk), then tamoxifen reduces the risk to 1 in 17 (6%).
- It is uncertain if this reduction in risk applies to women with a genetic error in the BRCA1 or BRCA2 gene as few women with genetic errors participated in the trials.

What are the side effects of tamoxifen?

- Common side effects of taking tamoxifen include hot flushes, vaginal discharge, vaginal dryness and bladder or urinary problems.
- Some women notice that their periods change (become irregular, lighter or stop altogether).
- Tamoxifen increases the risk of endometrial cancer in post-menopausal women - an additional 4 cases per 100 women per year of use.
- Tamoxifen increases the risk of thromboembolic events - an additional 4 cases per 1000 women per year of use
- Rarer side effects include cataracts and stroke.

Raloxifene

Raloxifene is suitable for post-menopausal women.

What effect does Raloxifene have on the chance of developing breast cancer?

- Raloxifene removes about 30% of a women's risk of breast cancer.
- If the chance of developing breast cancer in the next 5 years is 1 in 10 (10% risk), then raloxifene would reduce the risk to 1 in 14 (7%).
- It is uncertain if this reduction in risk applies to women with a genetic error in the BRCA1 or BRCA2 gene as few women with genetic errors participated in the trials.

What are the side effects of raloxifene?

- Raloxifene may be slightly safer than tamoxifen.
- Common side effects of taking raloxifene include hot flashes, vaginal dryness or irritation, joint and muscle pain and weight gain.
- Raloxifene increases the risk of thromboembolic events - an additional 3 cases per 1000 women per year of use
- Rarer side effects include cataracts and stroke.
- Raloxifene has **not** been shown to increase the risk of endometrial cancer

Contraindications: tamoxifen and raloxifene

- They are **not** recommended for women at standard (population) risk of breast cancer.
- They are **not** recommended for women who have had blood clots including deep vein thrombosis (DVT), or pulmonary embolism (PE), or stroke
- They are **not** recommended for women who take anticoagulants
- They are **not** recommended for women who smoke
- They are **not** recommended for women who are pregnant or planning a pregnancy
- They are **not** recommended for women who are breastfeeding

Pre-treatment checklist for clinicians:

- Ensure patient has had a normal mammogram or breast MRI within the last 12 months
- Clinical examination: including breast examination
- Full medical history: including current medication use/allergies and determine if there are any contraindications *(see above)*
- Drug history: some drugs can interfere with tamoxifen metabolism, especially antidepressants:
    - Venlafaxine (Effexor) seems to have the least **effect** on Tamoxifen metabolism
    - Strong inhibitors: Fluoxetine (Prozac), paroxetine (Paxil), bupropion (Wellbutrin) and duloxetine (Cymbalta)
    - Moderate inhibitors: citalopram (Celexa), escitalopram (Lexapro), desvenlafaxine (Pristiq), sertraline (Zoloft) and St John's Wort
    - Other drugs which may interfere with SERM include antipsychotics and antihistamines (a range of types).
- Record menopause status and symptoms
- For premenopausal women: check childbearing plans and if appropriate give advice to use effective non-hormonal contraceptives while on tamoxifen

Monitoring patients on RRM

- Patients should be monitored during their treatment, and this should usually be done by the prescribing clinician.
- Schedule: after first 2 months' of treatment
  then annually until treatment stopped
- Record: current symptoms, including vaginal bleeding for post-menopausal women
  any side effects
  result of routine mammograms
  ensure clinical breast examination has been performed.

Points for prescribing SERMs

- Indicate on the prescription that this is a non-PBS prescription for breast cancer prevention.
- Community pharmacies are permitted to prescribe up to 300 tablets at one time.
- Advise patients to contact a number of pharmacies as costs can vary substantially.
- Provide your patient with the consumer FAQ sheet so they are aware of what side effects to look for
  see http://canceraustralia.gov.au/sites/default/files/publications/rrm-risk-reducing-medication-for-women-at-increased-risk-of-breast-cancer-due-to-family-history_504af03f31630.pdf

Familial risk assessment tools:

A number of tools for assessing a woman's risk of breast cancer have been developed. They all have different strengths and limitations (see Fischer et al Journal of Medical Genetics 2013;50:360-367).

Tools to consider include:

Cancer Australia has developed an online tool that can be used to assess an individual woman's life time risk of developing breast cancer, although this tool has not been formally validated.
http://canceraustralia.gov.au/clinical-best-practice/gynaecological-cancers/familial-risk-assessment-fra-boc

The IBIS tool (also called the Tyrer-Cuzick model) is a validated downloadable tool that estimates a woman's 10-year and lifetime risk of developing invasive breast cancer. It also estimates the probability that a woman is a carrier of a mutation in the BRCA1 or BRCA2 gene.
http://www.ems-trials.org/riskevaluator/

The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) is a validated online tool that estimates a woman's risk of developing invasive breast cancer. It also estimates the probability that a woman is a carrier of a mutation in the BRCA1 or BRCA2 gene.
http://ccge.medschl.cam.ac.uk/boadicea/boadicea-web-application/

The Gail breast cancer risk assessment tool is a validated online tool that estimates a woman's 5-year and lifetime risk of developing invasive breast cancer.
http://www.cancer.gov/bcrisktool/

Further information

If you would like further information about these guidelines or would like to contact COSA or the COSA Familial Cancer Group please email us at cosa@cancer.org.au or phone (02) 8063 4100.