Breast cancer chemoprevention: a challenge for doctors and patients

Jo Marsden MD, FRCS and Chris Jacobs MSc, RN

The recently updated NICE familial breast cancer guidance now recommends discussion (within specialist genetic clinics) about chemoprevention with the selective oestrogen receptor modulators (SERMs) tamoxifen and raloxifene in women at high or moderate risk of developing breast cancer in the context of alternative approaches, such as risk-reducing surgery and surveillance. For both drugs the benefits and risks for other nonbreast outcomes/side-effects need to be discussed in order to ensure appropriate individualised advice. It is recommended that any written information provided encompasses absolute risk and benefit estimates.

Both tamoxifen and raloxifene reduce the risk of diagnosis of oestrogen-receptor positive (ER+ve) invasive breast cancer, the former in women irrespective of menopausal status and the latter in postmenopausal women only. Head-to-head comparison has shown risk reduction to be greatest with tamoxifen (38 per cent vs 23 per cent with raloxifene). NICE contraindicates the use of tamoxifen in women with a personal history of endometrial cancer and thromboembolic events; raloxifene is preferred as endometrial cancer diagnosis is not elevated and the risk of venous thromboembolic events, while increased, is less. Neither is recommended for women at high risk of breast cancer who have had bilateral mastectomy.

Eligibility for chemoprevention
Women at high or moderate risk of developing breast cancer are eligible. Women at high risk are those who carry a cancer-predisposing gene mutation or have more than a 30 per cent lifetime risk of breast cancer based on their family history. Those at moderate risk have between a 17 and 30 per cent lifetime risk.

Tamoxifen should be offered to premenopausal women and to postmenopausal women who have had a hysterectomy, and tamoxifen or raloxifene to postmenopausal women with a uterus, all for five years.

Women are not eligible if there is a history or high risk of thromboembolic disease or endometrial cancer, and women should stop tamoxifen at least six weeks before elective surgery (due to the associated risk from thromboembolic events).

Outstanding issues for planning chemoprevention management
Uptake of chemoprevention
NICE estimates a 25 per cent uptake of chemoprevention but this seems very optimistic. Recent evidence suggests that interest amongst high-risk women is low: 25 per cent on intention measures and 15 per cent for actual uptake. Exclusion of clinical trial participants gives an estimated uptake of less than 5 per cent. Poor uptake is attributed to unfavourable perception of the chemoprevention risk-benefit profile among women and health professionals alike.

Adherence with chemoprevention
The degree of risk reduction achieved with chemoprevention, while dependent on individual baseline risk of breast cancer, is equally dependent on treatment adherence. Despite assertions of the ‘good toxicity profile’ of tamoxifen and raloxifene, associated side-effects are one of the main reasons for poor and variable adherence in the clinical trial setting, eg less than 50 per cent adherence at three years.

The most troublesome side-effects are vasomotor symptoms, the management of which is difficult as HRT is contraindicated, leaving only less efficacious nonhormonal alternatives. Tamoxifen may cause menstrual irregularity in premenopausal women, and due to lack of any data regarding potential teratogenic effects it is advised to stop at least two months before trying to conceive.

Another factor not considered in the NICE guidance is variation in metabolic activity of tamoxifen according to menopausal status. In postmenopausal women, with the exception of its antioestrogenic effect on ER+ve cancer cells, tamoxifen has predominantly oestrogenic activity, accounting for the increased risk of thromboembolic events and endometrial cancer diagnosis but beneficial effects on bone-mineral density and inflammatory and serum lipid risk markers for cardiovascular disease.

In contrast antioestrogenic effects prevail in premenopausal women with a lack of stimulatory activity on the endometrium or coagulation but loss of bone-mineral density is increased significantly. There is a complete lack of data as to whether tamoxifen-induced bone loss is regained following its cessation.

Discussion of the benefits, limitations and side-effects of chemoprevention
The organisation of and demand for UK specialist genetics services means generally only patients at high risk of breast cancer are offered an appointment for genetic counselling. The NICE recommendation to discuss chemoprevention in moderate-risk women raises the prospect of risk assessment, prescription and monitoring outside of such centres, possibly within primary care. Genetic testing is unlikely to be available for women at moderate risk, raising challenges in how discussion of issues
surrounding chemoprevention will be managed. For those at moderate risk the benefits may be outweighed by chemoprevention-associated risks.

Balancing the risks and benefits of surgery and chemoprevention with breast-cancer risk

The decision to opt for chemoprevention will depend on the individual woman’s personal experience of breast cancer, baseline risk and available alternative risk-management options.

For the small proportion of BRCA1/2 mutation carriers (around 1 in 500 in the general population), the lifetime risk of breast cancer is up to 87 per cent (the steepest rise in risk between the ages of 40 and 49). BRCA1-related breast tumours are more likely to be oestrogen-receptor negative and the benefits of chemoprevention will be limited (some studies, however, suggest tamoxifen may reduce the risk of diagnosis in these women). Stratification of risk in women assessed to be at high risk who have not had a genetic test is difficult (these women have a greater than 30 per cent lifetime risk based on their family history).

For high-risk women, irrespective of whether they are proven gene mutation carriers, risk-management options are similar. NICE guidance recommends discussion of chemoprevention (reduces risk of diagnosis by up to 38 per cent) and the option of double mastectomy (reduces risk by 90 per cent). Some may be offered bilateral salpingo-oophorectomy to reduce the risk of ovarian cancer, which in premenopausal women also halves the risk of breast malignancy. MRI screening is only recommended in those with greater than 30 per cent chance of a cancer-predisposing gene mutation. These are challenging decisions for high-risk women.

Monitoring for side-effects and iatrogenic co-morbidities

If women commence treatment it is unclear who should manage the monitoring and follow-up for side-effects and iatrogenic co-morbidities. Specialist genetic clinics are not set up to provide on-going review of medication, and breast clinics need to focus their limited resources on the management of women with cancer.

Conclusion

It can be appreciated that the recently updated NICE guidance for familial breast cancer requires clarification with respect to planning appropriate referral, prescription and monitoring of women in whom chemoprevention is considered. It is too simplistic to discuss breast cancer risk reduction in isolation.

The UK Cancer Genetics Group is developing a patient information leaflet that may help patients who wish to consider chemoprevention but clinical pathways are yet to be agreed. Prevention in this clinical context aims to keep women well and promote self-management in primary care.

The selection of women for discussion of chemoprevention and optimal screening for iatrogenic side-effects and morbidities and who will provide this is still to be determined.

References


Declaration of interests

None to declare.

Miss Marsden is consultant breast surgeon, King’s College Hospital NHS Foundation Trust, London, and Chris Jacobs is consultant genetic counsellor in cancer genetics, Department of Clinical Genetics, Guy’s Hospital, London

Letters

If you have any issues you would like to air with your colleagues or comments on articles published in Prescriber, the Editor would be pleased to receive them and, if appropriate, publish them on our Forum page. Please send your comments to:

The Editor, Prescriber, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, or e-mail to prescriber@wiley.com