The evolving role of exemestane in the management of breast cancer

The role of therapies in the management of breast cancer is continuously changing. As research and development furthers, newer and more effective treatments are beginning to take the lead in cancer care, changing the role of tamoxifen.

Approximately 75–80% of breast cancer cases are oestrogen dependent. Reducing oestrogen levels can achieve regression of established disease and improve survival, especially in women with oestrogen receptor (ER)-positive tumours.

For years, treatment with oestrogen-receptor modulators like tamoxifen has been standard therapy for postmenopausal women with hormone receptor-positive breast cancer.

Recently, third-generation aromatase inhibitors (AIs) exemestane, anastrozole and letrozole have been shown to reduce recurrence and improve progression-free survival in metastatic breast cancer. Evidence is now emerging that they are also effective in the adjuvant setting, in the treatment of early breast cancer after surgery.

Exemestane: mode of action

Exemestane is a selective, highly potent AI. Unlike other oral AIs it is a steroidal aromatase inactivator that is distinguished from non-steroidal AIs by its configuration and mechanism.

The main sources of oestrogen in postmenopausal women come from the conversion of androgens into oestrogens, catalysed by the aromatase enzyme. Exemestane blocks this enzyme irreversibly and prevents aromatization, reducing circulating levels of oestrogen. Consequently, exemestane is considered to be an aromatase inactivator, rather than an inhibitor (Geisler et al, 1998).

Exemestane is extensively absorbed after oral administration. It is metabolized by oxidation (CYP3A4) and reduction (aldoketoreductase) to form secondary metabolites which are less active than the parent compound.

Exemestane is well tolerated and adverse events associated with its use are predictable and manageable. In clinical trials, adverse events were usually moderate, with one study in advanced breast cancer showing a withdrawal rate as a result of adverse events of 2.8% (Coombes et al, 2004b). The most frequent effects were hot flushes, nausea, fatigue, increased sweating and dizziness. Exemestane should not cause endometrial thickening or endometrial cancer, which are known effects after tamoxifen therapy (Goldstein, 2001).

Exemestane should not be given to premenopausal women and women who are pregnant. Dose modifications should be considered for patients taking concomitant CYP3A4 inducers, such as rifampicin.

Efficacy data with exemestane

Advanced breast cancer

Several clinical studies (Kaufman et al, 2000; Kvinnsland et al, 2000) have shown that exemestane provides effective and well-tolerated hormonal therapy for postmenopausal women with metastatic endocrine-dependent breast cancer refractory to tamoxifen.

A large, double-blind, randomized, multicentre study (Kaufman et al, 2000) showed that exemestane prolonged survival time, time to tumour progression and time to treatment failure compared with megestrol acetate in postmenopausal women with progressive advanced breast cancer who failed on tamoxifen. The study randomized 769 patients to exemestane (25 mg/day) (n=366) or megestrol acetate (40 mg four times daily) (n=403). Results demonstrated an overall objective response rate of 15.0% in patients treated with exemestane, and 12.4% in those patients treated with megestrol acetate (P=NS). A trend for higher response rates with exemestane was also seen in patients with visceral metastases (13.5% *vs* 10.5%).

The median survival time was significantly longer with exemestane (median was not reached) than with megestrol acetate (123.4 weeks; P=0.039), as were the median duration of overall success (objective response or stable disease >24 weeks; 60.1 *vs* 49.1 weeks; P=0.025), time to tumour progression (20.3 *vs* 16.6 weeks; P=0.037), and time to treatment failure (16.3 *vs* 15.7 weeks; P= 0.042).

These studies (Kaufman et al, 2000; Kvinnsland et al, 2000) confirm that exemestane offers a well-tolerated treatment option for postmenopausal women with progressive advanced breast cancer who experienced failure of tamoxifen. In 1999, Europe approved exemestane for the treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy.

Professor Nigel Bundred *is Professor in Surgical Oncology in the Department of Surgery, South Manchester University Hospital, Education and Research Building, 2nd Floor, Manchester M23 9LT*

Early breast cancer

Treatment with tamoxifen has dramatically improved survival in women with early breast cancer by reducing the risk of recurrence. However, around 15% of patients treated with adjuvant tamoxifen suffer a recurrence within 5 years (Early Breast Cancer Trialists' Collaborative Group, 2005). Studies with AIs have shown a reduced risk of recurrence compared to tamoxifen (Coombes et al, 2004b). Coombes et al (2004b) showed that switching to exemestane after 2–3 years of tamoxifen compared to continued treatment with tamoxifen improved disease-free survival by 27% in postmenopausal women with early breast cancer. Switching reduced the risk of recurrence by 30% and the risk of cancer in the contralateral breast by 50%. The clinical benefits of exemestane over tamoxifen were achieved without a detrimental impact on quality of life (Fallowfield, 2004).

These advances have resulted in the American Society of Clinical Oncology's (ASCO) most recent technology assessment of AIs recommending that 'adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer should include an AI in order to lower the risk of tumor recurrence' (Winer et al, 2004).

Optimizing outcomes

The greatest benefit from adjuvant hormonal therapy with tamoxifen in post-menopausal women with ER-positive early breast cancer is obtained during the first 2 years of treatment. After this, there is an increased risk that resistance to the drug will develop, and the benefits are outweighed by the risk of endometrial cancer and thromboembolic complications (Coombes et al, 2006).

There is growing evidence to support the hypothesis that switching patients to an AI after 2–3 years of tamoxifen therapy can help to prolong the benefits of anti-oestrogen therapy by overcoming the problems of resistance to tamoxifen, while reducing the risk of endometrial cancer. The Intergroup Exemestane Study (IES) investigated this (Coombes et al, 2006).

An updated analysis after a median follow up of 57.6 months confirmed that disease-free survival continued to be significantly greater with exemestane than with tamoxifen (hazard ratio 0.74, 95% confidence interval 0.64–0.85; $P<0.0001$) (Coombes et al, 2006). The time to contralateral breast cancer was also significantly greater with exemestane ($P=0.04$). The beneficial effects of exemestane treatment were not influenced by progesterone receptor status, nodal status or previous chemotherapy (Coombes et al, 2004a).

The results also showed a statistically significant halving in the incidence of new primary cancers other than breast cancer in women treated with exemestane ($P=0.003$). While the non-significant decrease in the incidence of endometrial cancer (five in the exemestane group *vs* 11 in the tamoxifen group) is consistent with expectations, the decreased incidence of other non-breast second primary cancers is not easily explained.

Exemestane was associated with higher incidences of arthralgia, diarrhoea and bone fractures (not statistically significant) than tamoxifen, whereas gynaecological symptoms, thromboembolic events, vaginal bleeding and muscle cramps were all more frequent in the tamoxifen arm.

Overall, this trial shows that in women treated with tamoxifen for 2–3 years there is a clear benefit of switching to exemestane in terms of reduced risk of recurrence including metastatic disease and a reduced risk of contralateral breast cancer, suggesting that switching will be the most appropriate strategy for adjuvant hormonal therapy in postmenopausal women.

Exemestane is currently the only AI with robust published data supporting its use after 2–3 years of tamoxifen in postmenopausal women with ER-positive early breast cancer (Coombes et al, 2006). Two smaller studies have used sequential aminoglutethimide after tamoxifen therapy (Boccardo et al, 2000) and anastrozole after tamoxifen therapy (Boccardo et al, 2005). Both trials suggested that the sequence might be better than tamoxifen alone, supporting the results of the IES. Overall, the hazard ratio for recurrence-free survival for switching from tamoxifen to an AI is 40%, compared to only 20% for use of an AI upfront.

Based on these results, the latest ASCO technology assessment of AIs suggests that postmenopausal women who have received 2–3 years of tamoxifen therapy may consider switching to an AI to complete a total of 5 years of adjuvant endocrine therapy (Winer et al, 2004).

In clinical practice, high-risk patients with a large postmenopausal tumour and four or more positive nodes are likely to benefit from upfront treatment with an AI because of their high risk of early recurrence. This is likely to be only about 10% of women with early breast cancer.

Other potential benefits of exemestane

One important benefit of prescribing tamoxifen for less than 5 years is a reduction in the risk of developing serious adverse effects, such as thromboembolic disease and endometrial cancer. However, tamoxifen's partial ER-agonist effects means that it has the advantage of protecting patients against the bone loss that can be a problem in postmenopausal women. One study found that after 5 years of treatment, patients in the tamoxifen group had a slight increase from baseline in mean bone mineral density (BMD) (+0.8%), whereas those who received placebo had a reduction in mean BMD (–0.7%), and the mean regression lines for the changes in BMD over 5 years differed significantly between the two groups ($P=0.0005$) (Love et al, 1992).

The reduction in circulating oestrogens that results from treatment with an AI could potentially lead to a decrease in BMD and an associated increase in the risk of fractures.

In the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial, which compared anastrozole with tamoxifen in postmenopausal early breast cancer, the fracture rate was significantly higher in the anastrozole group than in the tamoxifen group (P<0.0001) (Baum et al, 2003). In contrast, the initial analyses of IES found that the fracture rates for exemestane and tamoxifen were not significantly different (Coombes et al, 2006).

A randomized, double-blind, placebo-controlled study in women with early breast cancer or at low risk of relapse found no evidence that 2 years of exemestane treatment resulted in any difference in the rates of fracture compared to placebo (four fractures with exemestane *vs* five with placebo), and there were no detrimental effects on bone status in women who were osteopenic or osteoporotic (Lonning et al, 2005).

The average BMD-loss rate per year was 2.17% for exemestane compared to 1.84% for placebo in the lower (lumbar) spine (P=0.568). In the hip (femoral neck), annual bone loss was 2.72% *vs* 1.48% respectively (P=0.024).

Follow-up data showed that within 1 year of exemestane withdrawal the lumbar spine BMD tended to normalize, while the femoral neck BMD loss returned to normal and did not stabilize. This indicates that the effects of exemestane therapy on BMD may be reversible within 1 year after treatment withdrawal (Lonning et al, 2005).

Bone mass as measured by BMD is an important indicator of bone health. A 10% loss of bone mass can double the risk of vertebral fractures, and can result in a 2.5 times greater risk of hip fracture (Klotzbuecher et al, 2000). Hip fractures cause significant morbidity with reported mortality rates up to 20–24% in the first year after a hip fracture (Leibson et al, 2002). Therefore, limiting bone loss in this already at-risk group at the same time as offering women the best chance of surviving their breast cancer must be a focus of AI therapy.

Conclusions

Compelling clinical data on the use of AIs as adjuvant therapy are now changing the standard of care in postmenopausal women with ER-positive early breast cancer. Clinical studies have shown that exemestane provides effective and well-tolerated hormonal therapy for postmenopausal women with metastatic endocrine-dependent breast cancer refractory to tamoxifen.

A strategy of initiating hormonal therapy of breast cancer with tamoxifen, which prevents bone loss, followed by switching to an AI, seems to offer a rational approach to optimizing prevention of breast cancer recurrence and preserving bone density. A recent study (Coombes et al, 2006) showed that compared with continued treatment with tamoxifen in patients that were disease-free following 2-3 years treatment with tamoxifen, switching to exemestane improved disease free survival by 27% in postmenopausal women with early breast cancer. **BJHM**

Conflict of interest: Professor Bundred has been paid an honorarium for acting as a representative for all the AI pharma companies (Astra Zeneca, Novartis and Pfizer).

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KEY POINTS

- Exemestane is an aromatase inactivator which blocks androgens which cause oestrogen production.
- Exemestane is better than tamoxifen in the switch setting.
- Exemestane increases overall survival in postmenopausal women with hormone receptor-positive breast cancer.
- The main side effects of exemestane are similar to other aromatase inactivators but they are reduced.

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