Aromatase Inhibitors in Breast Cancer

Summary and Conclusions

TECHNOLOGY AND TARGET GROUP
Approximately 6,500 new cases of breast cancer are detected annually in Sweden. Early stages of the disease are treated surgically. Various types of adjuvant therapy may also be prescribed, e.g., hormonal agents. Despite adjuvant hormonal therapy, approximately 13 percent of the patients experience a relapse of breast cancer within 5 years. At recurrence a progress to advanced breast cancer, i.e., metastasis beyond the mammary gland and regional lymph nodes, is most often the case.

To determine whether a patient can potentially benefit from hormonal therapy, an investigation is conducted to assess whether the tumors are receptor positive, i.e., express estrogen and/or progesterone receptors. Approximately 70 percent of breast cancer tumors are receptor positive. Mainly it is estrogen that has a stimulating effect on tumor growth. When hormone production in the ovaries ceases after menopause, estrogen is produced mainly through hormonal conversion in peripheral tissue exerted by the enzyme aromatase. The administration of drugs acting as inhibitors of this enzyme reduce estrogen production, resulting in lower estrogen levels.

Previously, aromatase inhibitors had been approved only for second-line treatment of advanced breast cancer, after antiestrogen drugs (tamoxifen) no longer had an effect. Aromatase inhibiting drugs (anastrozole and letrozole) have now been approved also as first-line therapy for advanced breast cancer and as adjuvant therapy (anastrozole and letrozole) for early breast cancer. At present, it is difficult to determine the size of the potential target group.

PRIMARY QUESTION
To what extent are aromatase inhibitors more effective than antiestrogen drugs in adjuvant treatment of breast cancer and as first-line therapy for advanced breast cancer in postmenopausal women?

PATIENT BENEFIT
Advanced disease: Three randomized studies, including slightly over 1,800 patients in total, have compared aromatase inhibitors as first-line therapy for advanced breast cancer versus antiestrogen therapy (tamoxifen). Results from two of the studies have shown that the time to disease progress was 3 to 5 months longer in the group treated with aromatase inhibitors. The third study, however, reported no difference.

Adjuvant therapy: A randomized study of slightly more than 9,000 women, which compared aromatase inhibiting therapy (anastrozole) to tamoxifen therapy, showed after 68 months of followup that the group treated with anastrozole experienced 18.4 percent recurrence compared to 20.9 percent recurrence in the group treated with tamoxifen. These results provided a basis for approving anastrozole for adjuvant therapy in postmenopausal women with estrogen-receptor-positive breast cancer. A study that compared the aromatase inhibitor exemestane against tamoxifen showed, after 3 years of followup, results favoring the study group. Furthermore, a study that randomized just over 5,000 patients, after 5 years of tamoxifen therapy, to treatment with the aromatase inhibitor letrozole versus placebo showed an improvement in disease-free survival for the aromatase inhibitor treatment group. It is too early to assess the effects on overall survival, since these studies have not yet recorded a sufficient number of events (deaths).

Complications and side effects: The most common side effects associated with aromatase inhibitors are hot flushes, nausea, and genital dryness. Given the short followup times to date, fewer side effects have been reported with aromatase inhibitors than with tamoxifen, e.g., reduced risk for thromboembolic complications. However, adjuvant treatment with aromatase inhibitors affects bone mineral density and is associated with a higher incidence of fractures. Followup regarding long-term skeletal effects needs to be continued.

ECONOMIC ASPECTS
The drug cost for aromatase inhibiting therapy is approximately 14,000 Swedish kronor (SEK) annually versus slightly over 1,000 SEK for tamoxifen. Shifting from tamoxifen to aromatase inhibitors would increase the annual cost in Sweden by approximately 8 million SEK for treating advanced disease and by slightly over 100 million SEK for adjuvant therapy.

Several cost-effectiveness studies based on economic models have addressed the use of aromatase inhibiting drugs as first-line therapy in advanced breast cancer. Overall, they show that using aromatase inhibitors leads
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SBU’s appraisal of the evidence

In advanced disease, aromatase inhibitors as first-line therapy have been shown to extend the time to disease progression (Evidence grade 1)*.

Adjuvant therapy with aromatase inhibitors has been shown to reduce the risk for recurrence after followup of approximately 5 years (Evidence grade 1)*. No scientific evidence is yet available on long-term effects concerning survival and side effects (beyond 5 years). Only limited evidence is available on the cost effectiveness of using aromatase inhibitors.

References