Aromatase Inhibitors in Breast Cancer

SBU ALERT REPORT NO 2005-03 • 2005-03-02 • WWW.SBU.SE/ALERT

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

to a moderate increase in the cost per life-year gained compared with antiestrogen drugs. In one model study, the cost per life-year gained by adjuvant therapy with anastrozole was estimated at approximately 300 000 SEK based on calculations of 20 years and 8.2 million SEK based on calculations of 4 years. Little is known about the effects of treatment on future medical care consumption and survival, due to the short followup times in the studies from which the clinical data have been obtained. Consequently, reliable conclusions cannot be drawn from these model analyses.

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.

**Grading of the level of scientific evidence for conclusions.*
The grading scale includes four levels;
Evidence grade 1 = strong scientific evidence,
Evidence grade 2 = moderately strong scientific evidence,
Evidence grade 3 = limited scientific evidence,
Evidence grade 4 = insufficient scientific evidence.

References

1. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer (Cochrane Review). In: The Cochrane Library, Issue 4, 2004. Chichester, UK: John Wiley & Sons, Ltd.
2. Devita VT, Hellman S et al. Cancer. Principles and Practice of Oncology. 4th edition. JB Lippingcott Co. Philadelphia.
3. Rose C, Vtoraya O, Pluzanska A, Davidson N, Gershanovich M, Thomas R et al. An open randomised trial of second-line endocrine therapy in advanced breast cancer. Comparison of the aromatase inhibitors letrozole and anastrozole. Eur J Cancer 2003;39(16):2318-27.
4. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. N Engl J Med 2003;348(24):2431-42. Review.
5. Dranitsaris G, Leung P, Mather J, Oza A. Cost-utility analysis of second-line hormonal therapy in advanced breast cancer: a comparison of two aromatase inhibitors to megestrol acetate. Anticancer Drugs 2000;11(7):591-601.
6. Bonneterre J, Thurlimann B, Robertson JF, Krzakowski M, Mauriac L, Koralewski P et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol 2000;18(22):3748-57.
7. Nabholtz JM, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol 2000;18(22):3758-67.
8. Mouridsen H, Gershanovich M, Sun Y, Perez-Carrion R, Boni C, Monnier A et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol 2001;19(10):2596-606.
9. Lipton A, Ali SM, Leitzel K, Demers L, Harvey HA, Chaudri-Ross HA et al. Serum HER-2/neu and response to the aromatase inhibitor letrozole versus tamoxifen. J Clin Oncol 2003;21(10):1967-72.
10. Ellis MJ, Coop A, Singh B, Mauriac L, Llombert-Cussac A, Janicke F et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol 2001;19(18):3808-16.
11. Baum M, Budzar AU, Cuzick J, Forbes J, Houghton JH, Klijn JG et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 2002;359(9324):2131-9.
12. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349(19):1793-802.
13. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350(11):1081-92.
14. Buzdar AU. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial: an update. Clin Breast Cancer 2004;5 Suppl 1:S6-S12.
15. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF et al; ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365(9453):60-2.
16. Dranitsaris G, Verma S, Trudeau M. Cost utility analysis of first-line hormonal therapy in advanced breast cancer: comparison of two aromatase inhibitors to tamoxifen. Am J Clin Oncol 2003;26(3):289-96.
17. Karnon J, Johnston SR, Jones T, Glendenning A. A trial-based cost-effectiveness analysis of letrozole followed by tamoxifen versus tamoxifen followed by letrozole for postmenopausal advanced breast cancer. Ann Oncol 2003;14(11):1629-33.
18. Karnon J, Jones T. A stochastic economic evaluation of letrozole versus tamoxifen as a first-line hormonal therapy: for advanced breast cancer in postmenopausal patients. Pharmacoeconomics 2003;21(7):513-25.
19. Simons WR, Jones D, Buzdar A. Cost-effectiveness of anastrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer. Clin Ther 2003;25(11):2972-87.
20. Marchetti M, Caruggi M, Colombo G. Cost utility and budget impact of third-generation armatase ihibitors for advanced breast cancer: a litterature-based model analysis of costs in the italian national health service. Clin Ther 2004;26(9):1546-61.
21. Hillner BE. Benefit and projected cost-effectiveness of anastrozole versus tamoxifen as initial adjuvant therapy for patients with early-stage estrogen receptor-positive breast cancer. Cancer 2004;101(6):1311-22.

SBU – The Swedish Council on Technology Assessment in Health Care

SBU is an independent public authority which has the mandate of the Swedish Government to comprehensively assess healthcare technology from medical, economic, ethical, and social standpoints. SBU Alert is a system for identification and early assessment of new methods in health care.

P.O. Box 5650, SE-114 86 Stockholm, Sweden • alert@sbu.se

This summary is based on a report prepared at SBU in collaboration with:

- **Eva Liliemark** (expert), MD, PhD, Medical Products Agency,
- **Cindy Wong** (expert), MD, PhD, Medical Products Agency,
- Prof. **Jonas Bergh** (reviewer), Karolinska University Hospital, Stockholm
- **Carsten Rose** (reviewer), Chairman, Dept. of Oncology, Lund University Hospital, Lund

The complete report is available only in Swedish.