



Aromatase inhibitors in the treatment of early ER-positive breast cancer in post-menopausal women

SBU ALERT REPORT | EARLY ASSESSMENT OF NEW HEALTH TECHNOLOGIES

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Summary and conclusions

Radical operations are performed on 4500 post-menopausal women with primary breast cancer each year in Sweden. In this postmenopausal group approximately 85% have an ER-positive tumor with no sign of distant spread. Adjuvant hormonal therapy is prescribed to at least 90% of these women after surgery (circa 4400), aimed at preventing recurrence and breast cancer related death.

Since most of these tumour cells are dependent on oestrogen to be able to divide, anti-oestrogen therapy reduces the risk rates of recurrence and improves survival. From 1980 until 10 years ago, tamoxifen (TAM) was the drug of choice for ER-positive breast cancer. Over the last 10 years aromatase inhibitors (AI) have been introduced for postmenopausal patients, but long-term follow-up data on treatment and side-effects have only recently become available.

In 2005, SBU released an "Alert Report" regarding AI treatment for breast cancer (www.SBU.se/200503). The conclusion of that report was that AI (letrozol, anastrozol and exemestan) when given as first-line treatment for advanced breast cancer, could delay progression of the disease compared to TAM (high quality of evidence). Adjuvant therapy with AI also reduce the risk for recurrence based on studies with follow-up up to 5 years (high quality of evidence). Scientific documentation on long-term survival and side-effects, however, was not available at that time. Furthermore little was known about cost-effectiveness.

In this report we evaluate the effects of adjuvant therapy with AI on disease-free survival (DFS) and overall survival (OS) after five or more years of follow-up, including available off-treatment data, in various management strategies for early breast cancer in post-menopausal women with primary breast cancer. Furthermore we report the incidence of side-effects during AI treatment including death without recurrence, uterine cancer, deep venous thromboembolisms as well as effects on the heart and

brain vasculature. We also report on health-related quality-of-life, cognitive symptoms and the predictive values of clinically relevant biomarkers.

Economic considerations

The prices of AI have decreased by more than 90 percent since the release of the patents. At a willingness-to-pay of at least 300,000 Swedish kronor per QALY (quality-adjusted life year), the alternative of changing to exemestane after 2-3 years treatment with tamoxifen has a high probability of being cost-effective compared to continuing with TAM. Anastrozole and letrozole have a high probability of being cost-effective treatment alternatives regardless of the willingness to pay per QALY.

Ethical aspects

Breast cancer is a serious disease that is often fatal if not treated. Mortality rates have fallen over the years because of early diagnosis and modern systematic adjuvant therapy such as hormone treatment. Aromatase inhibitor therapy has become the adjuvant treatment of choice for postmenopausal women with oestrogen-sensitive breast cancer due to its verified increase in disease-free survival.

In the majority of cases, the side-effects of AI are acceptable. However, approximately one third of women receiving AI suffer from side-effects that reduce their quality of life, consequently leading to difficulties with completing treatment. This negative effect on the patient's quality of life is similar to what is experienced with TAM although the type of adverse events differ somewhat. There is some concern as to the risk for cognitive side-effects associated with hormonal therapy including AI, but data is scarce and the evidence is of low quality, making it difficult to give adequate information to the patient. Low adherence has been seen with all forms of hormonal therapy, emphasizing how important it is to inform

the patient about potential side-effects and their effects on quality-of-life before recommending and commencing treatment. This enables the patient to make an informed decision when accepting the treatment suggested. The negative effects of hormonal treatment on quality-of-life usually appear during the first year of treatment and disappear once the drug is discontinued. A follow-up soon after starting a new therapy allows physicians to identify problematic side-effects early on; enabling them to provide timely advice to the patient about coping with the unwanted symptoms or even about alternative therapies.

In conclusion, there are no obvious ethical problems with adjuvant AI therapy. AI is probably cost-effective but moderately severe side-effects may cause the patient to stop treatment prematurely which could however lead to inferior treatment results.

Conclusions

- ▶ Mono- or sequential therapy with AI increases disease-free survival (DFS) compared to TAM. Prolonged AI therapy after five years of TAM increases DFS compared to placebo.
- ▶ Monotherapy with AI increases overall survival (OS), sequential or prolonged AI therapy however, does not obviously increase OS.
- ▶ AI therapy increases the risk for fractures compared to TAM, but decreases the risk for uterine cancer and deep vein thrombosis.
- ▶ No significant differences between AI and TAM are seen regarding side-effects on the heart and brain vasculatures, or death without recurrence.
- ▶ Scientific evidence is insufficient to be able to say if there are any clinically relevant differences between AI and TAM regarding their effect on cognitive function (thought and memory function).
- ▶ No significant differences between AI and TAM have been seen regarding health-related quality-of-life.

- ▶ The presence of oestrogen receptors (ER) in a tumour is predictive of a positive result from hormone treatment whether it be with AI or with TAM. However the difference in effect between AI and TAM can not be predicted by ER. The presence of progesterone receptors (PgR), proliferation indicators, or overexpression of HER2 have no predictive value regarding success of treatment with AI versus TAM.
- ▶ Before the patent period expired, treatment with AI probably cost no more than 430,000 SEK per QALY regardless of whether it was given as mono-, sequential or prolonged therapy. The price of AI, and thus the cost per QALY, has since fallen considerably almost certainly making AI cost-effective.

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