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Anastrozole versus progestins/tamoxifen

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1. Introduction

Systemic therapy of breast cancer was introduced in 1896 by means of surgical ovariectomy [1]. Endocrine treatment is now widely accepted in advanced breast cancer with positive oestrogen or progesterone receptor status indicating endocrine dependency of the disease. Tamoxifen has been the treatment of choice for more than twenty years, due to it's favourable efficacy/tolerability ratio [2]. Several years ago, the third generation aromatase inhibitors have been introduced in the clinics [3]. Anastrozole is a potent selective non-steroidal aromatase inhibitor which can be administered orally as a once daily dose.

The effects of anastrozole on *in vivo* aromatisation was evaluated in postmenopausal women with advanced breast cancer testing 1 or 10 mg per day. The whole body aromatase activity was determined by measuring the isotope ratio of androgens to oestrogens in the plasma and the urine after injection of an isotope-labelled androstendione and oestrone. The mean suppression of aromatisation was 96.7 and 98.1% respectively. Plasma oestrogen levels are lowered nearly to the detecton limit of a highly sensitive assay [4–6].

2. Anastrozole versus megestrol acetate

The efficacy of anastrozole as second-line treatment has been investigated by two large randomised multicentre trials in postmenopausal women with advanced breast cancer. Megestrol acetate was chosen as a comparative drug because it was considered as a standard endocrine treatment in patients with disease progression on tamoxifen in the United States. Aminoglutethimide has been used as second-line treatment in many other countries [7]. However, there are no published data comparing anastrozole with aminoglutethimide. Patients with a poor performance status and known oestrogen receptor-negative disease or exposure to more than one chemotherapy regimen for advanced disease were excluded from the studies. Eligible patients were randomised to receive either anastrozole 1 or 10 mg daily or megestrol acetate 40 mg 4 times daily. The primary endpoint was time to progression. Both trials showed no statistically significant difference between either 1 or 10 mg anastrozole or megestrol acetate for any primary efficacy endpoint.

A retrospective survival analysis based on the combined data of the two studies including 764 patients was reported with a median follow-up of 31 months (Fig. 1). The 1 mg treatment group showed a significant overall survival advantage compared with megestrol acetate with a Hazard Ratio of 0.78 ($P < 0.025$) and an increase in overall survival of 4.2 months. Patients on the 10 mg anastrozole arm were favoured with a Hazard Ratio of 0.83 ($P = 0.0095$) and an increased median overall survival of three months. At the time of the survival analysis the data was mature, with 62% of patients dead. The toxicity results also favoured anastrozole [8–10].

Based on the encouraging results of the previous studies anastrozole was investigated in 2 similarly designed randomised trials, performed in the USA and Canada (trial 30) and in Europe, Australia, New Zealand, South America and South Africa (trial 27). Postmenopausal patients with locally advanced or metastatic disease and indication for endocrine therapy as first-line treatment were randomised to receive either anastrozole 1 mg or tamoxifen 20 mg daily. The study was designed to demonstrate an equivalence in the time to progression and response rate and to allow for a combined analysis. Patients with known hormone receptor-negative disease were not eligible for the study. Characteristics of the patients and the pre-treatment data were well balanced between the treatment groups. However, there was an important difference beween the trials: 89% of the patients in the North American Trial were known to have receptor-positive disease compared with only 45% in trial 27. These differences reflect the

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different pattern of care at that time in the different countries participating in the trial. The results of both studies were published with a median follow-up of 18.2 months. They showed that anastrozole was at least as effective as tamoxifen. Furthermore, in trial 30 (Fig. 2), with most patients having oestrogen and/or progesterone receptor-positive tumours, a significant difference in favour of anastrozole in terms of the primary endpoint time to progression was shown. Time to progression was approximately doubled for patients receiving anastrozole compared with patients receiving tamoxifen (11.1 versus 5.6 months, $P = 0.005$).

In trial 27 (Fig. 3), patients with positive oestrogen receptor status had a longer time to progression in an unplanned subgroup analysis.

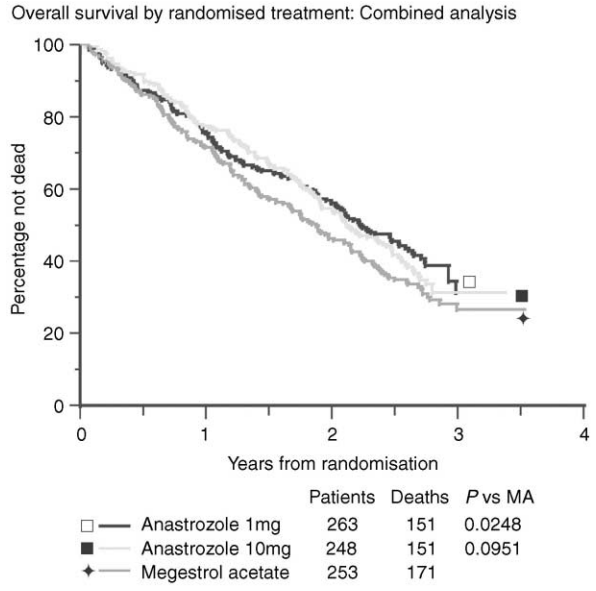
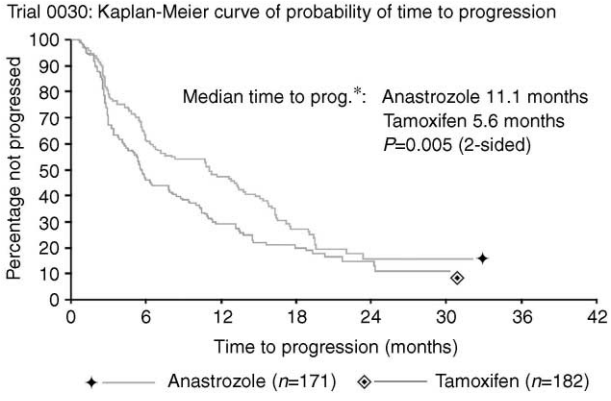


Fig. 1. Anastrozole versus megestrol acetate.



*Hazard ratio (Tamoxifen: Anastrozole) 1.44, lower CL 1.16.
Study 'powered' for equivalence.
Median follow-up of 18 months. 71% progression

Fig. 2.

A prospectively planned combined analysis of both trials including 1021 patients has been performed. Subgroup analysis including receptor status, previous endocrine treatments, visceral metastases, liver metastases, bone metastases and age was performed. Only the subset of hormone receptor positive disease (Fig. 4) showed a statistically significant advantage for anastrozole in terms of median time to progression ($P = 0.022$, two-sided test).

The analysis of tolerability showed a similar number and pattern of side-effects of both drugs with two important exceptions: thromboembolic events and vaginal bleeding were less frequently seen following anastrozole treatment [11–13].

A Spanish study including 238 patients with metastatic disease, positive receptor status and no previous adjuvant hormonal therapy also showed favourable results for anastrozole when compared with tamoxifen. More than 50% of these patients had visceral involvement as the predominant site of disease. The overall response rate was 34% for anastrozole and 27% for tamoxifen. Clinical benefit rate was 82% and 55%, respectively ($P = < 0.03$). The median time to progression for anastrozole was 12.3 versus 5.3 months for

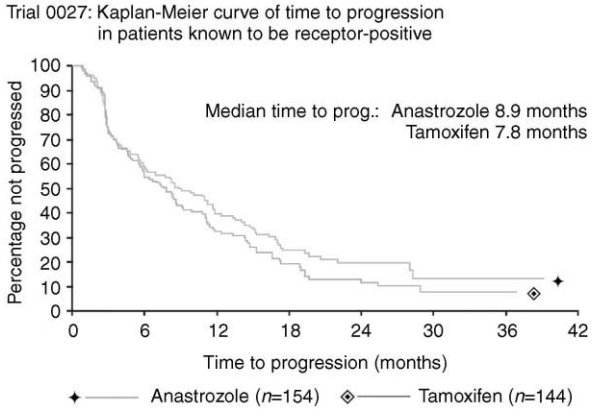
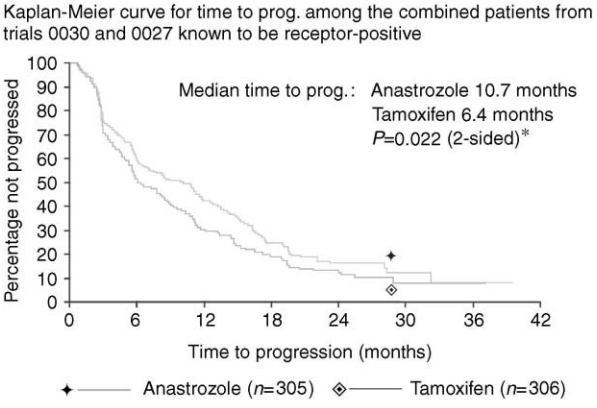


Fig. 3.



*Based on a retrospective analysis

Fig. 4.

tamoxifen with a hazard ratio of 0.77 (95% CI: 0.56-0.91; $P = < 0.05$). These results are in line with the results of trial 30 and the results of patients with hormone receptor-positive disease in trial 27. An updated analysis also showed a survival advantage for patients randomised to first-line anastrozole treatment [14].

2.1. Sequence of endocrine treatments

In advanced disease, endocrine active drugs are frequently given in sequence to obtain maximal palliative benefit in patients with hormone receptor-positive disease and/or with relevant benefit from previous endocrine therapies (3). This successful strategy has also been investigated in trials 27 and 30. Questionnaires were sent out to all investigators collecting data on the sequential use of anastrozole or tamoxifen after the randomised treatment. A similar number of patients received the cross-over treatment and similar numbers of questionnaires were sent back for patients randomised to tamoxifen or anastrozole. The results of these questionnaires showed a similar response rate for both drugs irrespective whether tamoxifen or anastrozole has been given as first-line treatment [15]. Similar findings were also seen for the subgroup of patients with visceral involvement as the dominant site of disease [16].

To summarise: The results of these three studies show at least equivalence of anastrozole when compared with tamoxifen in an unselected patient population and superiority of anastrozole in patients known to have hormone receptor-positive disease. Tolerability is also better with anastrozole. Available data from the cross-over of both drugs indicate no apparent disadvantage of the subsequent tamoxifen treatment when anastrozole is given as first-line therapy in advanced breast cancer.

3. Future directions

Anastrozole has also been tested as adjuvant treatment versus tamoxifen (both alone and in combination with tamoxifen) in a large trial of postmenopausal patients with early breast cancer. First encouraging results were recently presented in Ref. [17]. They confirm the effectiveness and good tolerability of the drug. Further maturation of efficacy and long-term tolerability is needed, but the overall drug profile make anastrozole an excellent candidate to be tested in the preventive setting.

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References

1. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: Suggestions for a new method of treatment of illustrative cases. *Lancet* 1896, **ii**, 104–107.
2. Fossati R, Gonfalonieri C, Torri V, *et al*. *J Clin Oncol* 1998, **16**, 3439–3460.
3. Thuerlimann B. Hormonal treatment of breast cancer: new developments. *Oncology* 1998, **55**, 501–507.
4. Koeberle D, Thuerlimann B. Anastrozole: pharmacological and clinical profile in postmenopausal women with breast cancer. *Expert Rev Anticancer Ther* 2001, **1**, 169–176.
5. Plourde PV, Dyroff M, Dukes M. Arimidex: a potent and selective fourth-generation aromatase inhibitor. *Breast Cancer Res Treat* 1994, **30**, 103–111.
6. Geisler J, King N, Dowsett M, *et al*. Influence of anastrozole (Arimidex), a selective, non-steroidal aromatase inhibitor, on in vivo aromatisation and plasma oestrogen levels in post-menopausal women with breast cancer. *Br J Cancer* 1996, **74**, 1286–1291.
7. Castiglione-Gertsch M, Pampallona S, Varini M, *et al*. Primary endocrine therapy for advanced breast cancer to start with tamoxifen or with medroxyprogesterone acetate. *Ann Oncol* 1993, **4**, 735–740.
8. Jonat W, Howell A, Blomqvist C, *et al*. A randomized trial comparing two doses of the new selective aromatase inhibitor (Arimidex) with megestrol acetate in postmenopausal patients with advanced breast cancer. *Eur J Cancer* 1996, **32A**, 404–412.
9. Buzdar AU, Jones SE, Vogel CL, Wolter J, Plourde P, Webster A. A phase III trial comparing anastrozole (1 and 10 milligrams), a potent and selective aromatase inhibitor, with megestrol acetate in postmenopausal women with advanced breast carcinoma. *Cancer* 1997, **79**, 730–739.
10. Buzdar AU, Jonat W, Howell A, *et al*. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: Results of a survival update based on a combined analysis of data from two mature phase III trials. *Cancer* 1998, **83**, 1142–1152.
11. Nabholtz JM, Buzdar A, Pollak M, *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. *J Clin Oncol* 2000, **18**, 3758–3767.
12. Bonneterre J, Thuerlimann B, Robertson JFR, *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**, 3748–3757.
13. Buzdar A, Bonneterre J, Nabholtz JM, *et al*. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: Findings Highlight the importance of receptor status assessment prior to treatment indication. *Ann Oncol* 2000, **11**(Suppl. 4), Abstract 990.
14. Milla-Sontos A, Milla L, Rallo L. Phase III trial of anastrozole vs tamoxifen in postmenopausal patients with hormone-dependent advanced breast cancer. *Eur J Cancer* 2001, **37**(Suppl. 5), Abstract 0–11.
15. Thuerlimann B, Robertson JFR, Bonneterre J, *et al*. Effcacy of tamoxifen following Arimidex (anastrozole) as first-line treatment for advanced breast cancer in postmenopausal women. *Breast Cancer Res Treat* 2000, **64**, Abstract 162.
16. The ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of post menopausal women with early breast cancer: first results of the ATAC randomized trial. *The Lancet* **359**, 2131–2139.
17. Data on file. 2001, AstraZeneca, Macclesfield, UK.