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Aromatase inhibitors as adjuvant therapies in patients with breast cancer☆

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Abstract

There is increasing evidence that endocrine therapy has an important role in patients with oestrogen receptor positive breast cancer. Several large meta-analyses have reinforced the value of both ovarian ablation and tamoxifen in improving survival. Over the past decade, aromatase inhibitors have become the treatment of choice for second-line therapy of metastatic breast cancer, and the third generation inhibitors have now an established reputation for good patient tolerability. Early studies indicated that aminoglutethimide/hydrocortisone could benefit postmenopausal patients with primary breast cancer, and in 2001, the ATAC study showed that the third generation aromatase inhibitor, anastrozole, seemed superior to tamoxifen in that anastrozole-treated patients had a longer disease-free survival. Other studies will report on the relative merits of the steroidal inhibitor exemestane as well as non-steroidal letrozole. The exact duration and sequencing of treatment, together with the long-term effects on bone are at present, unknown.

Keywords: Aromatase; Breast cancer; Adjuvant treatment

1. Introduction

Several strategies have been adopted to ablate endocrine organs, reduce steroid synthesis or block hormones as adjuvant therapy for breast cancer. The first were surgical or radiotherapeutic ovarian ablation in premenopausal women. The EBCTCG overviews showed that the overall survival rate following adjuvant ovarian ablation is similar to that of chemotherapy [1,2]. This overview analysis also showed that tamoxifen significantly reduced recurrence by 45% and mortality by 32% in premenopausal women, similar to the situation in postmenopausal patients. For patients with oestrogen receptor-rich tumours who received tamoxifen for 5 years, the reduction in recurrence in mortality was 50% and 28%, respectively.

With the development of aromatase inhibitors, it became apparent that patients with metastatic disease could respond to aminoglutethimide [3] or second and third generation inhibitors after either failure to respond to adjuvant tamoxifen or relapse whilst on tamoxifen [4]. These studies paved the way for new concepts in the use of aromatase inhibitors for adjuvant therapy. This article reviews some of the early and current adjuvant treatment strategies for patients with early breast cancer.

2. Adjuvant therapies using first generation aromatase inhibitors

Aminoglutethimide was introduced in the 1970s when it was discovered that it could inhibit the conversion of cholesterol to oestrogen [3]. Several studies indicated that aminoglutethimide was capable of inhibiting many enzymes, including aromatase, in the steroid synthesis pathway [3]. Randomised trials showed that first line aminoglutethimide, when combined with hydrocortisone, led to an approximately similar response rate as tamoxifen (∼20%) in patients with advanced breast cancer [3].

In view of this, we commenced an adjuvant study in which 354 oestrogen receptor positive or negative, postmenopausal patients with histologically confirmed axillary nodes were randomised to receive 250 mg aminoglutethimide, four times daily and 20 mg hydrocortisone twice daily or placebo [5,6]. With a minimum of 5 years follow-up, no overall benefit for aminoglutethimide, in terms of event-free or overall survival was seen. However, examination of the survival curves indicated that there was a benefit for aminoglutethimide and hydrocortisone treated patients in terms of event-free survival up to approximately 4 years ($P = 0.005$) but this benefit reduced over time ($P = 0.015$). There was

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a similar but less pronounced benefit in terms of overall survival up to approximately 4 years ($P = 0.052$) but this subsequently disappeared as well ($P = 0.055$) [5].

The rate of relapse was similar in the two treatment groups. There was a borderline significant treatment interaction with oestrogen receptor status which showed that for overall survival, the benefits of receiving aminoglutethimide and hydrocortisone were greater in oestrogen receptor positive patients ($P = 0.054$).

In this trial, there was a significant increase in toxicity (with respect to lethargy, ataxia and skin rash) for patients who received aminoglutethimide and hydrocortisone. Three patients developed agranulocytosis.

Despite the side-effects, this study indicated that adjuvant therapy with aromatase inhibitors could have a beneficial effect. In retrospect, it was somewhat surprising that such a consistent effect was observed with relatively small numbers of patients.

3. Adjuvant therapy using second generation aromatase inhibitors—4-OH androstenedione (formestane)

Formestane was first described as a potential treatment in animal models of breast cancer by Brodie et al. [7]. Subsequently, formestane was shown to be an effective treatment for patients with metastatic breast cancer [8] and larger trials led to the demonstration of its value as second and third line treatment. One potential disadvantage of formestane was the fact it had to be administered intramuscularly.

In the first adjuvant trial, which began in 1990, patients with oestrogen receptor positive primary breast cancer were randomised to receive either neoadjuvant or adjuvant formestane for a total of 18 months.

The results indicated that formestane was active in oestrogen receptor positive patients. Under UICC criteria, 36% patients responded to neoadjuvant formestane. In this pilot study, patients suffered very few side effects [9].

Subsequently, we analysed the disease-free survival and overall survival in these patients after a minimum of 5 years follow-up [10]. There was no evidence of a survival benefit from the neoadjuvant regime but there was a significant reduction in the incidence of metastases in responders compared with non-responders ($P < 0.01$). There was also a reduction in the need for extensive surgery in responding patients since fewer patients went on to have a mastectomy.

4. Third generation aromatase inhibitors

Third generation inhibitors have been used either in the neoadjuvant or adjuvant setting, including the steroidal, irreversible (type 1) inhibitor, exemestane, and non-steroidal, reversible (type 2) inhibitors, anastrozole and letrozole.

A series of small neoadjuvant studies using the third generation inhibitors suggested that aromatase inhibitors may be more effective than tamoxifen [11], although this was not confirmed in a recent study (Harper-Wynne et al., in press). A neoadjuvant study has also been carried out using exemestane [11]. In this study, patients were given 25 mg daily for 3 months prior to surgery and tumour volume was reduced by 86% with 83% of patients responding to treatment.

More recently, a study by Ellis [12] has shown that letrozole is more effective in the treatment of primary breast cancer than tamoxifen. This is principally due to its beneficial effect on steroid receptor positive tumours which are also either epidermal growth factor receptor positive or HER-2 positive than those which are growth factor receptor negative ($P = 0.0004$).

Two groups have initiated studies exploring the role of sequential treatment with aromatase inhibitors after the completion of 5 years of tamoxifen and a further two groups have explored the use of aromatase inhibitors after 2–3 years of tamoxifen. Two further groups have explored the role of first-line aromatase inhibitors in comparison to tamoxifen and one of these [13] has recently reported. The aromatase inhibitors used in these studies are the steroidal aromatase inhibitor, exemestane, and the non-steroidal inhibitors, letrozole and anastrozole.

The National Surgical Adjuvant Breast and Bowel Project Group (NSABP) has launched the B33 trial. In this trial, after completion of 5 years tamoxifen, patients are randomised to either exemestane for 2 years or placebo. The International Collaborative Cancer Group (ICCG) as part of the Breast International Group (BIG) is conducting a study in which patients are randomised after 2–3 years of tamoxifen to exemestane or to continue tamoxifen to complete a total of 5 years endocrine therapy.

With regards to letrozole, the BIG is conducting a four-arm trial of 5 years tamoxifen versus 5 years letrozole as compared with a combination of an initial 2 years tamoxifen followed by 3 years letrozole or the opposite sequence.

The ATAC group has recently reported the results after a median follow-up of 33.3 months [13]. In this study, 9366 patients were randomised to receive anastrozole, tamoxifen or the combination, anastrozole plus tamoxifen. At 3 years, disease-free survival was significantly greater in patients receiving anastrozole (89.4%) compared to those on tamoxifen (87.4%) (hazard ratio 0.83; 95% CI 0.71 to 0.96; $P = 0.013$). As expected, this difference was evident in oestrogen receptor positive patients but not in oestrogen receptor negative patients.

There are two important features to note, however, 1079 first events, 850 (79%) were recurrences or new contralateral tumours. 229 (21%) were deaths without recurrence, although there was no major difference in all cause mortality between the arms of the study. A striking reduction (HR 95% CI: to $P = 0.007$) was seen in primary contralateral breast cancers. There was little difference in recurrence rates, distant metastases or primary contralateral breast cancers between the tamoxifen and the combination arms.

The study has also reported comparisons of short term side effects. Anastrozole was associated with a significant reduction in hot flushes (35% as opposed to 40% on tamoxifen), vaginal discharge, vaginal bleeding, ischaemic cerebrovascular events, venous thromboembolic events, including deep venous thrombosis and endometrial cancer.

However, musculoskeletal disorders and fractures were significantly more common with anastrozole than with tamoxifen. Interestingly, the sites of fractures appeared more frequently to be in the spine than in the hip.

Weight gain was similar in all three arms, being approximately 2.5% over 2 years. One important feature of this trial was the observation that anastrozole was associated with significantly fewer withdrawals from treatment than tamoxifen, including fewer withdrawals related to adverse events ($P < 0.0001$).

5. Future studies of adjuvant aromatase inhibitors in breast cancer treatment

Although at the moment, tamoxifen remains the gold standard for the adjuvant endocrine treatment of breast cancer [14], it may well be that, in order to minimise the risks of endometrial carcinoma and pulmonary embolism, anastrozole or other third generation aromatase inhibitors become the treatment of choice in the future. However, a possible limitation of these compounds will be the incidence of osteoporosis and fracture. Future studies will have to address these issues, perhaps by randomised trials of the use of concomitant biphosphonates or calcium supplements.

Further issues include the duration and sequencing of aromatase inhibitors, as well as the issue of cross-resistance between steroidal and non-steroidal inhibitors, since studies in patients with metastatic disease suggest that there may be a role for using both classes in certain patients [15]. Finally, it is possible that different subsets of patients benefit from anti-oestrogens and aromatase inhibitors as has been indicated by neoadjuvant studies [16].

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