Risks versus benefits in the clinical application of aromatase inhibitors

P E Goss
Department of Medical Oncology & Hematology, Princess Margaret Hospital, 610 University Avenue, 5-303
Toronto, Canada M5G 2M9

Abstract
Third-generation aromatase inhibitors are able to reduce circulating plasma estrogen concentrations in postmenopausal women to below detectable limits and significantly inhibit aromatase, the enzyme responsible for estrogen synthesis, in normal breast tissue and breast tumors. Their role in the treatment of advanced breast cancer is well established and their use in adjuvant therapy is currently being explored. On the basis of these trials, evaluation of these inhibitors in the prevention of breast cancer may be appropriate. Aromatase inhibitors have non-specific toxic side effects including (but not limited to): asthenia, headache, nausea, peripheral edema, fatigue, vomiting and dyspepsia. In addition, certain endocrinological side effects in postmenopausal women are notable, namely hot flushes and vaginal dryness. In advanced breast cancer, these side effects result in treatment withdrawal in few (<4%) women. Of concern, however, are the potential long-term endocrinological side effects in women receiving treatment as first-line adjuvant therapy or in sequence or combination with tamoxifen or other selective estrogen receptor modulators (SERMs). Current studies of adjuvant treatments for breast cancer in healthy women are carefully evaluating, in addition to general toxicities, the effects on bone, lipid metabolism, cardiovascular risk, quality of life and menopausal symptoms. Careful evaluation of all-cause morbidity and mortality is necessary to plan trials and justify long-term use of aromatase inhibitors in the treatment or prevention of breast cancer in healthy women.

Introduction
Tamoxifen has played a central role in the endocrine treatment of advanced and early breast cancer over the past few decades. Furthermore, the largest clinical trial investigating its use for the primary prevention of breast cancer has recently been completed by the National Surgical Adjuvant Breast and Bowel Project (NSABP) (Fisher et al. 1998). Although a reduction in the incidence of breast cancer and clinical bone fractures has been demonstrated, concerns regarding adverse effects, including an increase in the risk of endometrial cancer and thromboembolism (Fisher et al. 1998), have tempered reaction to these results. The third-generation oral aromatase inhibitors have been demonstrated, in both preclinical and clinical settings, to be highly potent and specific inhibitors of estrogen synthesis (Giudici et al. 1988, Bhatnagar et al. 1990, Evans et al. 1992, Iveson et al. 1993, Wouters et al. 1993, Plourde et al. 1994, Goss et al. 1995). As monotherapy, their use has been explored primarily in the treatment of advanced breast cancer in postmenopausal patients with disease progression after initial tamoxifen therapy (Buzdar et al. 1996, Bergh et al. 1997, Dombernowsky et al. 1998, Gershmanovich et al. 1998, Jones et al. 1998, Goss et al. 1999). A preliminary evaluation of toxicities observed suggests that these agents are very well tolerated. Thus their potential role in the management of early-stage breast cancer and in prevention merits further investigation.

In this paper, the efficacy and short-term toxicities of third-generation inhibitors are briefly reviewed and issues associated with prolonged reduction of postmenopausal estrogen concentrations are discussed. A way to explore the efficacy and all-cause potential morbidity and mortality from these agents is offered. It is hoped that this will provide a basis for the future rational expansion of the clinical indications of this important new class of endocrine therapeutic agents.

The physiologic role of postmenopausal estrogens
Estrogens are known to play a key role in multiple physiological functions in women. They have important actions on bone and lipid metabolism and cardiovascular function, and diffuse effects on other target organs, including skin, the urogenital system, and endometrium...

The extent to which low postmenopausal estrogen concentrations contribute to the integrity of these multiorgan functions is uncertain, and the impact of further reduction of plasma estrogen in postmenopausal women needs to be carefully explored. Adverse effects on bone, lipid profile and vasomotor symptoms may occur. In contrast, a reduction in breast and endometrial cancer risk may result. Thus the net clinical usefulness of plasma estrogen reduction through use of aromatase inhibitors needs to be carefully determined.

**Current clinical indications for third-generation aromatase inhibitors**

Both the non-steroidal (anastrozole, letrozole, and vorozole) and steroidal (exemestane) third-generation oral inhibitors have been substantially evaluated in preclinical models and, more recently, in patients with advanced breast cancer. Randomized phase III clinical trials have now been completed and data are available on their use compared with megestrol acetate and aminoglutethimide in combination with hydrocortisone (Buzdar et al. 1996, Bergh et al. 1997, Dombernowsky et al. 1998, Gershmanovich et al. 1998, Goss et al. 1999). All three of the non-steroidal inhibitors have demonstrated at least equivalent, and probably superior, clinical utility compared with megestrol acetate, and a superior toxicity profile. The principal side effects of these agents compared with those of megestrol acetate are presented in Table 1. This table reports ‘adverse events on study’ although, in these patients with advanced breast cancer, it is not clear to what extent these adverse events are related to the drug or the underlying disease. However, some side effects compatible with their mechanism of action are notable. For example, increased weight gain, dyspnea, and thromboembolic events, are associated more with the use of megestrol acetate (Henderson 1991). In contrast, a slight trend towards greater gastrointestinal toxicity and hot flushes is apparent for the inhibitors. Overall, however,

| Table 1 | Common adverse events (%) reported in three phase III trials of non-steroidal aromatase inhibitors compared with megestrol acetate |
|-------------------|-------------------------------|-------------------------------|-------------------|
| Adverse event     | Anastrozole (1 mg)† | Letrozole (2.5 mg)* | Vorozole (2.5 mg)** |
|                   | ANA  | MA  | LET  | MA  | VOR  | MA  |
| Asthenia          | 16   | 7   | -    | -   | -    | -   |
| Nausea            | 16   | 11  | 10.9 | 9.0 | 20.4 | 11.0 |
| Dyspnea           | 9    | 21  | 9.2  | 16.4| 14.2 | 25.1 |
| Headache          | 13   | 10  | 12.6 | 9.0 | 10.7 | 10.1 |
| Arthralgia        | -    | -   | 13.2 | 7.9 | 13.3 | 7.5  |
| Fatigue           | -    | -   | 10.9 | 11.1| 15.1 | 17.6 |
| Peripheral edema  | 5    | 11  | 8.6  | 7.9 | 10.7 | 11.0 |
| Pain              | 11   | 12  | 2.9  | 4.8 | 21.3 | 15.0 |
| Weight increase   | 2    | 12  | 2.3  | 8.5 | 1.3  | 13.7 |
| Vomiting          | 9    | 6   | 7.5  | 5.3 | 6.7  | 4.0  |
| Dyspepsia         | -    | -   | 5.2  | 5.8 | -    | -    |
| Hot flushes       | 12   | 8   | 5.7  | 3.7 | 19.6 | 7.0  |

†Reported in >10% of patients, regardless of causibility (Buzdar et al. 1996).
*Reported in >5% of patients, regardless of causibility (Dombernowsky et al. 1998).
**Reported as events occurring in >10% of patients (Goss et al. 1999).
- Not available; ANA, anastrozole; LET, letrozole; MA, megestrol acetate; VOR, vorozole.
fewer than 4% (range 2.7-3.1%) of patients withdrew from study because of adverse events experienced when receiving aromatase inhibitors (Buzdar et al. 1996, Dombernowsky et al. 1998, Goss et al. 1999). Likewise, a summary of five clinical trials with the steroidal inhibitor, exemestane (Lonning et al. 1997), indicated that toxicities with the 25 mg/day dose were minimal and confined to androgenic effects (including hypertricosis, hair loss, hoarseness and acne; 4%), hot flushes (11%), increased sweating (4%) and nausea (3%). With the obvious clinical efficacy and excellent side-effect profile, the therapeutic index and clinical utility of the third-generation aromatase inhibitors in the treatment of advanced breast cancer are unquestionable.

Future potential clinical applications of third-generation aromatase inhibitors

Following the results achieved by the use of aromatase inhibitors after tamoxifen in advanced breast cancer, the relative efficacy and tolerability of these agents are being further explored in comparison with tamoxifen as initial therapy for patients with advanced breast cancer. In addition, a number of large international adjuvant therapy trials exploring their role in the treatment of early breast cancer are already established or have recently been launched (Table 2). These trials explore the ability of aromatase inhibitors to prevent recurrent (local and metastatic) breast cancer and new breast primary tumors. This has led to the consideration of aromatase inhibitors as potential primary agents of breast cancer prevention in healthy women. The application of aromatase inhibitors in other less common benign disorders such as gynecostasia, adrenal hyperplasia, precocious puberty, and other more rare conditions have unique requirements of assessment of clinical utility, and will not be discussed further in this paper.

Evaluation of optimal dose schedule and duration of treatment

As previously mentioned, the physiological role of low levels of estrogens in postmenopausal women is as yet undetermined. It will therefore be important to determine the minimal dose and duration of therapy with aromatase inhibitors required to demonstrate a positive clinical effect and minimize any untoward end-organ toxicities. It may be that a partial reduction of plasma estrogen concen-

| Table 2 List of key adjuvant trials with aromatase inhibitors |
|------------------|-----------------|-----------|
| **Trial**     | **Design**      | **Design** |
| Anastrozole    | TAM (5 years)   | vs        |
| ATAC           | TAM + ANA (5 years) vs ANA (5 years) |
| ARNO           | TAM (2 years) → TAM (3 years) vs TAM (2 years) → ANA (3 years) |
| Letrozole       | TAM (5 years) vs 2-arm vs 4-arm |
| BIG/FEMTA      | LET (5 years) vs 2-arm vs 4-arm |
| MA.17          | TAM (5 years) → LET (5 years) vs 4-arm |
| Exemestane     | TAM (5 years) vs 4-arm |
|                | TAM (2 years) → EXE (3 years) |

Compounds: ANA, anastrozole; EXE, exemestane; LET, letrozole; PLAC, placebo; TAM, tamoxifen.
Trials: ATAC, Arimidex, tamoxifen alone or in combination; ARNO, Arimidex-nolvadex; BIG/FEMTA, Breast International Group/Femera-tamoxifen.
trations is as effective at reducing the incidence of breast cancer as a more complete estrogen depletion. This may also preserve, or have less impact on, other end-organ systems such as the cardiovascular system and bone. This concept is illustrated in Fig. 1. Clearly, pilot clinical trials using surrogate endpoints, exploring different doses and evaluating toxicities would be of great value before the launch of large-scale clinical trials of primary prevention with aromatase inhibitors.

**Evaluation of long-term toxicities**

Common toxicities associated with third-generation aromatase inhibitors have already been outlined in this paper. Clearly, in a population of healthy women, the toxicity profile is likely to differ, as present data regarding side effects come largely from patients with metastatic breast cancer. In addition, few data are available on long-term toxicities. However, it is reasonable to hypothesize that reduction of plasma estrogen in postmenopausal women will have a number of beneficial effects, and possibly detrimental effects, on certain target tissues. Furthermore, these effects may be influenced significantly by the use of the inhibitors alone, in sequence after tamoxifen (or another SERM), or in combination with tamoxifen (or another SERM) (Table 3).

For example, in male rats vorozole was found to impair skeletal modeling and decrease bone mineral density (Vanderschueren et al. 1997). In contrast, SERMs have both estrogen agonist and antagonist properties and the relative balance between these effects varies for each compound. For example, raloxifene has been shown to increase bone mineral density in postmenopausal women and not stimulate the endometrium (Delmas et al. 1997). Thus one could postulate that raloxifene given in combination with an aromatase inhibitor might lead to a neutral impact on the bone - negating the potential negative effect of the aromatase inhibitor.

The various adjuvant trials with aromatase inhibitors (Table 2) provide an opportunity to evaluate efficacy with respect to breast cancer recurrence, incidence of contralateral breast cancer and disease-free and overall survival, together with end-organ toxicities. In each of the studies listed in the Table, nested companion studies are in progress to determine the specific impact on various organ systems. For example, the international MA.17 trial is exploring the use of an aromatase inhibitor after patients have been exposed to tamoxifen for 5 years, and incorporates a detailed assessment of bone, including the incidence of clinical fractures, bone mineral density and bone metabolism biomarkers. Likewise, a detailed study of lipid metabolism along with cardiovascular endpoints

[Table 3: Potential interaction between aromatase inhibitors (AI) and SERMs]

<table>
<thead>
<tr>
<th></th>
<th>Uterus</th>
<th>Vaginal mucosa</th>
<th>Bone</th>
<th>Lipid/cardiovascular</th>
<th>Cognition/Alzheimer’s</th>
<th>Thromboembolic disease</th>
<th>Breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SERM→AI</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+?</td>
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<tr>
<td>SERM+AI</td>
<td>+/-</td>
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<td>+?</td>
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</tbody>
</table>

+ Beneficial; – detrimental; +/- neutral.
SERM→AI, sequential use; SERM+AI, combined use.
will be undertaken. Furthermore, the impact on overall quality of life is being assessed using the SF 36 quality of life tool and a menopause-specific questionnaire (McHorney et al. 1993). The latter scale assesses four domains - vasomotor, psychological, physical and sexual aspects.

Other investigators have utilized risk benefit assessments for patients participating in primary prevention studies. For example, Nease & Ross (1995) developed a decision-making model for patients enrolling in the NSABP P-1 Tamoxifen Breast Cancer Prevention Trial. In that study, they used a decision-analytic model that was based on available data regarding the efficacy of tamoxifen in women with breast cancer and its presumptive toxicities. They then extrapolated the model for use in healthy women, to determine the circumstances under which the potential benefits of enrolling in the P-1 trial were likely to outweigh the potential risks (Fig. 2). It was concluded that, for a 50-year-old woman with a breast cancer risk twice that of the average women of this age, the P-1 trial offered an increase in life expectancy of about 9 days; and for women aged 35-60 years who met the minimum risk of breast cancer requirement, the trial increased life expectancy by 8 to 9 days. The authors therefore concluded that ‘although women at increased risk for breast cancer should be aware of the likely overall benefit associated with entry into the trial, for most women, entry into P-1 was unlikely to alter substantially their length of life, in either a beneficial or harmful manner.’

By the same token, before the initiation of the BIG/FEMTA and MA.17 trials (see Table 2), a careful analysis of all-cause morbidity and mortality for the use of aromatase inhibitors as adjuvants in early breast cancer patients was conducted. A model was constructed and from it expected change in life-expectancy was determined. Various scenarios (base, best, middle, worst) were then generated by inserting certain assumptions with respect to breast cancer mortality, cardiovascular and bone risk. It was determined that unless a ‘no effect’ on breast cancer mortality was observed, benefit would likely outweigh risk across a spectrum of postmenopausal ages.

In any case efficacy data from trials of aromatase inhibitors in early breast cancer that are planned or in progress, together with companion studies providing benefit/risk data with respect to end-organ toxicity, should enable a rational model to be designed with respect to the implementation of third-generation aromatase inhibitors.

![Figure 2 Risk/benefit analysis of entering the NSABP P-1 trial. Decision analysis model representing the alternatives (shown as branches out of the decision node (A)) and the uncertain events (shown as branches out of the round chance nodes) involved in the decision to enter or decline entry into the Breast Cancer Prevention Trial. Death from causes noted; (open diamond), survival during a 1-year period. MI, Myocardial infarction; PE, pulmonary embolism. Reprinted with permission from Nease & Ross (1995).]
in breast cancer prevention. This may allow the results of these adjuvant therapy trials to be extrapolated directly to various subpopulations of healthy women, and possibly to the general population of postmenopausal women.

**Potential inclusion/exclusion criteria for use of third-generation aromatase inhibitors in breast cancer prevention**

Data have emerged in the published literature that suggest that women with increased bone density, increased breast density, and high plasma estradiol concentrations are all associated with an increased risk of breast cancer (Wolf 1976, Saftlas & Szklo 1987, Boyd et al. 1995, Cauley et al. 1996 Thomas et al. 1997a,b, Zhang et al. 1997). It is tempting to postulate that these three parameters are correlated and that a paradigm may be developed for postmenopausal women in which a prolonged ‘high estrogen’ or ‘low estrogen’ state may be defined based on these three parameters (Table 4). It may be possible to determine the validity of such a paradigm within the context of a breast cancer prevention trial. If it were proved correct, this would enable women in the general population to be selected for either estrogen reduction strategies such as the use of SERMs or aromatase inhibitors or, conversely, for estrogen replacement therapy in the context of traditional hormone replacement therapy. Such an approach might enable prevention from morbidity and mortality of the three most common illnesses in postmenopausal women, namely, cardiovascular disease, osteoporosis and breast cancer. If this paradigm were confirmed, further studies of the etiology of ‘high estrogen’ - ‘low estrogen’ states in women would clearly be of importance in determining possible causation of breast cancer.

**Conclusion**

In summary, third-generation aromatase inhibitors are well tolerated and their relative benefit in the treatment of advanced breast cancer is unquestionable. Outstanding issues for their use as adjuvants and in primary prevention in healthy women include determining the optimal dose schedule and duration of therapy, all-cause morbidity and mortality risk with long-term use, and overall risk benefit.

**References**


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**Table 4** Estradiol (E₂) concentrations, bone density, breast density and breast cancer risk

<table>
<thead>
<tr>
<th>Breast cancer risk</th>
<th>High</th>
<th>Low</th>
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<tbody>
<tr>
<td>Lifetime estrogen exposure/E₂ level</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Bone density</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Breast density</td>
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