Status of aromatase inhibitors in relation to other breast cancer treatment modalities

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Abstract
Aromatase is one of the key enzymes possibly linked with the perpetuation or even initiation of breast cancer. Modulation of its activity by the new generation inhibitors has resulted in increased responses and improved therapeutic ratio compared with those of parent aromatase inhibitors. More recent trials have shown promising results with regard to improved therapeutic ratio compared with what is seen with presently accepted second-line hormonal approaches. Present data and laboratory research indicate that new aromatase inhibitors have the potential to play an important role as adjuvants, and possibly in the prevention of human breast cancer. It is probable that it may be as adjuvants that their real therapeutic strength in terms of a beneficial impact on survival may be realized. The absence of estrogen agonist activity of new aromatase inhibitors on lipid and bone metabolism calls for more clinical studies having late mortality in breast cancer survivors as the ultimate outcome objective; in this regard, interaction of new aromatase inhibitors with new selective estrogen receptor modulators looks promising. Achievement of these outcomes, and understanding of interactions with other therapies, await the termination of present trials and the start of new initiatives.

Introduction

Ragaz: Aromatase inhibitors - relation to other treatments


Old trials of aromatase inhibitors: aminogluthethimide

Post-mortem observations in epileptic children whose deaths were associated with aminogluthethimide treatment, used then as a sedative for epilepsy, identified adrenal insufficiency as a factor responsible for their death (Cash et al. 1967). ‘Side effect turned into benefit’ publications from the early 1970s proposed testing aminogluthethimide as a form of ‘medical adrenalectomy’ (Hughes & Burley 1970, Griffith et al. 1973) in attempts to achieve biochemical ablation of the adrenals, practiced then on a large scale surgically. Aminogluthethimide was later confirmed to be an effective inhibitor of several enzymes of the cytochrome P450 family that are active in the cleavage of the cholesterol molecule (Fishman et al. 1967, Santen et al. 1977). The inhibition also included aromatase - the key enzyme involved in the conversion of andros-tenedione to estrogens in the adrenals and extra-adrenally; thus a reduction of circulating estrogens follows. Suppression of aromatase by the use of aminogluthethimide would be particularly effective in postmenopausal women, in whom more than 80% of estrogen is derived from the periphery, outside the adrenal glands (Santen et al. 1977). Other enzymes subsequently confirmed to be affected by aminogluthethimide were desmolase and hydroxylase, both responsible for suppression of gluco-corticoids and mineralocorticoids (Fishman et al. 1967, Santen et al. 1977, Samojlik et al. 1977). Hence, aminogluthethimide requires the use of cortisone and, at times, of mineralocorticoids.

Early studies confirmed responses to aminogluthethimide to be similar to those to other hormonal modalities (Gale et al. 1976, 1994, Harvey et al. 1979, Ragaz 1981, Santen et al. 1981, Corkery et al. 1982, Lipton et al. 1982, Smith et al. 1982, Powles et al. 1984, Ingle et al. 1986, Rose et al. 1986). Once comparability with adrenalectomy or hypophysectomy was confirmed (Harvey et al. 1979, Santen et al. 1981), the surgical ablative procedures were rapidly eliminated from breast cancer treatment.

Aminogluthethimide and tamoxifen

As a result of good tolerance, tamoxifen emerged rapidly, in the mid 1970s, as the first-line hormonal agent for stage IV breast cancer, with a therapeutic ratio significantly better than that of estrogens, androgens, progestins or surgical procedures. After the establishment of the efficacy of medical adrenalectomy, several trials compared aminogluthethimide and tamoxifen (Ragaz 1981, Corkery et al. 1982, Lipton et al. 1982, Smith et al. 1982, Powles et al. 1984, Ingle et al. 1986, Rose et al. 1986, Gale et al. 1994). Most confirmed similar response rates and response durations in stage IV disease, but greater complexity and more side effects with aminogluthethimide. Also, in the late 1970s and early 1980s, it was postulated that reduced concentrations of estrogen in response to aminogluthethimide may improve the response to tamoxifen (Ragaz 1981), and several combination trials started (Ragaz 1981, Corkery et al. 1982, Smith et al. 1982, Powles et al. 1984, Ingle et al. 1986, Rose et al. 1986). Although the outcome has not been improved by use of the combinations, responses to aminogluthethimide were documented in a substantial number of patients who failed to improve with tamoxifen. The main reported side effects of aminogluthethimide included loss of energy, postural hypotension, skin rash, hematological abnormality, sleepiness and gastric upset (Santen et al. 1981, Ragaz et al. 1984, Messeche et al. 1985). In attempts to reduce the toxicity, several trials tested the possibility of using low-dose aminogluthethimide (Bonneteer et al. 1985, Harris et al. 1986, Upright et al. 1990). Despite a slight reduction in side effects, the aminogluthethimide regimen remained complex, with tamoxifen remaining the first-line choice of therapy.

Aminogluthethimide and pituitary hormones

Early studies of aminogluthethimide confirmed interaction with other enzymes of the cytochrome P450 family, and with some of the pituitary hormones (Fishman et al. 1967, Santen et al. 1977, Samojlik et al. 1977). One of the early trials (Delmas et al. 1997) observed not only previously documented significant changes in dehydroepiandrosterone and thyroid-stimulating hormone, but also, during the first 7 months of therapy, a significant mean increase in follicle-stimulating hormone (FSH) over basal values.
and a subsequent decrease in FSH to the pretreatment levels. Fluctuation of estrogen in the opposite direction - a primary stimulus for FSH fluctuations - was suspected. Increasing concentrations of estrogens in the latter part of therapy were thus considered a primary cause for the resistance to amino-glutethimide (Ragaz 1981).

The early amino-glutethimide data emphasize the interaction of aromatase inhibitors with other endogenous hormones. The interaction has recently been confirmed to involve cytokines also (Miller et al. 1997). These complex interactions may constitute the main mode of action of aromatase inhibitors, affecting the hormonal milieu on a large scale. The full extent of this interaction has yet to be determined.

New aromatase inhibitors (Table 1)

Animal experiments by Brodie and colleagues in the late 1970s were the first successful efforts, after the introduction of aminoglutethimide, to expand on the concept of selective aromatase inhibition (Brodie et al. 1977). The group developed a compound, 4-hydroxyandrostenedione (4-OHA), that was shown to inhibit significantly the conversion of 4-androstenedione to estradiol in human placental and rat ovarian microsomes, and to be more potent and more specific than amino-glutethimide (Brodie et al. 1977, Coombes et al. 1984). Subsequently, modification of the aromatase suppressive domain resulted in the development of two types of new generation aromatase inhibitors. The first were steroidal analogs, including the above mentioned 4-OHA (formestane, lentaron) given intramuscularly and exemestane administered orally (Evans et al. 1992). Formestane has been used extensively in the past several years (Coombes et al. 1984, 1992 Goss et al. 1986, and the more recently developed exemestane is undergoing clinical testing (Lonning et al. 1997, Thurlimann et al. 1997). The second class of aromatase inhibitors included a group of non-steroidal analogs, of which roglethimide and fadrazole (the so-called second generation aromatase inhibitors) were developed first (Foster et al. 1985, Beretta et al. 1990, Dowsett et al. 1990, Lonning et al. 1991, Trunet et al. 1992); they were followed subsequently by triazole inhibitors (the third generation aromatase inhibitors), which include anastrozole, letrozole and vorozole (Bhatnagar et al. 1990, Dowsett 1990, Lipton et al. 1990, Johnstone et al. 1994, Plourde et al. 1994, Geisler et al. 1996, Trunet et al. 1996).

All new aromatase inhibitors exhibit substantially greater potency of aromatase suppression in vivo - varying from 500 to 10 000-fold - compared with amino-glutethimide (Table 1). In addition, all are more specific aromatase suppressors, with substantially less pronounced effect on desmolase or hydroxylase, and no clinically or biochemically detectable suppression of glucocorticoids or aldosterone.

Table I Overview of aromatase inhibitors: potency and specificity of aromatase inhibition compared with aminoglutethimide†

<table>
<thead>
<tr>
<th>Aromatase suppression</th>
<th>Potency</th>
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<tr>
<td></td>
<td>Specificity</td>
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<tr>
<td>First generation</td>
<td></td>
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<tr>
<td>Aminoglutethimide</td>
<td>+/-</td>
</tr>
<tr>
<td>Testolactone</td>
<td>+/-</td>
</tr>
<tr>
<td>Second generation</td>
<td></td>
</tr>
<tr>
<td>Formestane</td>
<td>++</td>
</tr>
<tr>
<td>Fadrazole</td>
<td>++</td>
</tr>
<tr>
<td>Roglethimide</td>
<td>++</td>
</tr>
<tr>
<td>Third generation</td>
<td></td>
</tr>
<tr>
<td>(Vorozole)*</td>
<td>+++</td>
</tr>
<tr>
<td>Exemestane</td>
<td>+++</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>+++</td>
</tr>
<tr>
<td>Letrozole</td>
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*Production discontinued by the manufacturer.

Clinical use of hormones

At the time of those developments, tamoxifen had been firmly established as a first-line hormone, both in adjuvant settings and in stage IV disease. In metastatic disease, the therapeutic sequence after tamoxifen included progestins as second-line therapy, followed by aminoglutethimide as third (Upright et al. 1990). The challenge of new aromatase inhibitors was to see if they could emerge as superior to any of the established hormonal treatments. The first to be tested were aminoglutethimide and progestins. In all these trials, eligibility criteria included prior therapy with tamoxifen.

New aromatase inhibitors and aminoglutethimide

Both vorozole and letrozole were tested recently against aminoglutethimide. The Letrozole International Trial Group (Marty et al. 1997) undertook a randomized trial of letrozole in two doses, 2.5 mg and 0.5 mg, in comparison

*Production discontinued by the manufacturer.
with aminogluthethimide 250 mg by mouth twice a day with hydrocortisone 30 mg/day. The greatest objective responses and response durations were seen in the high-dose letrozole arm of the trial. Overall survival also showed a trend for improvement ($P=0.06$). With fewer side effects, letrozole 2.5 mg clearly emerged as superior to aminogluthethimide.

The Multicenter Vorozole Group performed a randomized trial of vorozole 2.5 mg by mouth in comparison with aminogluthethimide 250 mg by mouth twice a day with hydrocortisone 30 mg/day, until disease progression or death (Bergh et al. 1997). There was a trend for improved objective response rates with vorozole, but response duration and overall survival were similar. However, tolerability was improved, as significantly more aminogluthethimide-treated patients than vorozole-treated patients had drug-related side effects (53% compared with 31%, $P<0.001$), with more patients forced to discontinue aminogluthethimide because of side effects (10% compared with 3%, $P<0.001$).

**New aromatase inhibitors and progestins**

**Progestins**

The two principal progestins, the orally used megestrol acetate (Megace), and the intramuscularly administered medroxyprogesterone acetate (Provera), have been shown in the past trials to have comparable effectiveness and response rates (Muggia et al. 1968, Robustelli Della Cuna et al. 1978, Canetta et al. 1983, Alexieva-Figusch et al. 1984, Cavalli et al. 1984, Muss et al. 1988, 1990, Henderson 1990). Several randomized trials of Megace compared with tamoxifen, or Provera compared with tamoxifen, have also shown comparability of these agents with tamoxifen, not only in the metastatic setting but also in adjuvant therapy (Muss et al. 1988, Henderson 1990). However, the side effects of progestins were more significant, and included weight gain and related increased appetite, fluid retention and edema, menorrhagia and thromboembolic episodes. Less frequently, muscle cramps, sweating, nausea with or without vomiting, and hypercalcaemia were seen. According to old reports, the most troublesome side effect - the weight gain - is seen in its mild form of <4.55 kg in up to 50% of all patients; up to 9.1 kg gain is seen in 30%, and up to 13.64 kg in 12% of patients (Muggia et al. 1968, Robustelli Della Cuna et al. 1978, Canetta et al. 1983, Alexieva-Figusch et al. 1984, Cavalli et al. 1984, Muss et al. 1988, 1990, Henderson 1990). Response rates of both Megace and Provera can be increased with the escalation of the dose, but the side effects of both progestins are also dose dependent (Robustelli Della Cuna et al. 1978, Canetta et al. 1983, Alexieva-Figusch et al. 1984, Cavalli et al. 1984, Muss et al. 1990). These greatly limit the more uniform use of high-dose progestins.

All three triazole aromatase inhibitors, vorozole, anastrozole and letrozole, have been tested in large, multicenter phase III clinical trials with the most commonly used progestational agent, megestrol acetate.

**Randomized trials - vorozole compared with megestrol acetate**

The trial of vorozole, the first of the three aromatase inhibitors, showed no difference in objective response rate (Goss et al. 1999). Whereas a trend for a greater response duration was seen with vorozole (18.2 compared with 12.5 months), no difference was detected in the duration of median survival (26 compared with 28.7 months). More patients discontinued megestrol than vorozole because of adverse effects (6.2% compared with 3.1%), and significantly more megestrol-treated patients had weight gain (14% compared with 1%). Despite these disadvantages the documented improved therapeutic ratio, vorozole was subsequently withdrawn from further clinical testing.

**Randomized trials - anastrozole compared with megestrol acetate**

The International Anastrozole Trial undertook a randomized comparison between megestrol acetate 160 mg, anastrozole 1 mg, and anastrozole 10 mg. Analysis of the combined results of the merged North American and European trials showed comparable response rates and response durations, but a recent update (Buzdar et al. 1997) showed, at 31 months follow up, a significant overall survival benefit with anastrozole 1 mg compared with megestrol acetate (median survivals 26.7 and 22.5 months, 2-year overall survivals 56.1% and 46.3%; $P=0.02$). Fewer side effects were seen with anastrozole, in particular, weight gain (2% compared with 12% of patients). Other side effects, including thromboembolic episodes, gastrointestinal disturbances, hot flushes and vaginal dryness, were all comparable. Outcome analysis of anastrozole 10 mg compared with 1 mg confirmed the absence of a dose-response relationship, with the optimum dose of anastrozole being 1 mg. In conclusion, anastrozole 1 mg emerged as a significantly superior agent, regarding both efficacy and therapeutic ratio.

**Randomized trials - letrozole compared with megestrol acetate**

A letrozole trial was also finalized and reported recently (Dombernowsky et al. 1998). The trial involved two doses of letrozole, 2.5 and 0.5 mg, randomized against megestrol 160 mg. Results confirmed a significantly better overall response rate and median response durations in...
In summary, all three trials of aromatase inhibitors confirmed their equal or better efficacy, with fewer side effects, compared with aminogluthethimide or megestrol, with a substantially improved therapeutic ratio. These data were the required impetus leading to the acceptance of the new aromatase inhibitors as second-line agents for stage IV disease, after tamoxifen. In addition, trials comparing new aromatase inhibitors with tamoxifen as first-line agents and as adjuvants were started. Of interest is that, although the therapeutic ratio of new aromatase inhibitors over aminogluthethimide or Megace in individual trials was better, the ranges of objective response rates or their durations were similar (Table 2). The main therapeutic benefit of aromatase inhibitors given as second-line therapy in metastatic disease, therefore, is derived mostly from the improved tolerance and fewer side effects. Thus stage IV may not be the best model with which to test for efficacy, as the disease is then advanced and resistance to hormones probably widely developed. Therefore, in order to detect the more substantial aromatase inhibition that manifests in vivo as more significant survival benefits or cures, it will be necessary to perform testing from adjuvant or preventive perspectives.

### New aromatase inhibitors and tamoxifen

**Tamoxifen**

The most recent, 1995, overview (Early Breast Cancer Trials’ Collaborative Group 1998) confirmed the beneficial survival impact of tamoxifen in patients with clinical stage I-II breast cancer. Compared with the 1990 analysis (Early Breast Trials’ Collaborative Group 1992), the current analysis provides more definitive data in at least four areas:

1. **Definitive superiority in estrogen receptor-positive patients for trials of 5 compared with less than 5 years duration;**
2. **Significant impact of estrogen receptor status;** and, in estrogen receptor-positive patients treated with tamoxifen for 5 years:
   1. **Definitive survival advantage in young women younger than 50 years of age;**
   2. **A substantial effect in the presence of adjuvant chemotherapy.**

While the advantage of 5 years rather than less than 5 years duration of tamoxifen therapy is firmly established, the preliminary results of two recent studies testing the prolongation of tamoxifen therapy - 10 years compared with 5 years of tamoxifen - showed no difference. The recently concluded National Surgical Adjuvant Breast and Bowel Project (NSABP) report showed, in node-negative patients, overall survival of 94% and 96% with 10 and 5 years of tamoxifen, respectively (National Cancer Institute 1996). Similar observations were also made in a much smaller Scottish trial of node-positive and node-negative breast cancer patients. As a result, no further testing of tamoxifen treatment durations greater than 5 years is being considered in North America. The UK adjuvant tamoxifen-longer (ATLAS) and adjuvant tamoxifen -treatment offer more (ATTOM) trials are, therefore, the only current trials of tamoxifen treatment duration beyond 5 years, with more than 20 000 patients expected to enter the trials. Because of the importance of the question of the optimum duration of tamoxifen treatment, analysis of the findings of the ATLAS and ATTOM trials may be required before a final verdict on this issue is reached.

### Table 2 Ranges of reported objective response rates and durations among second-line hormones of different categories used after tamoxifen

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Objective response rate (%)</th>
<th>Response duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglutethimide†</td>
<td>(12-30)</td>
<td>13-24</td>
</tr>
<tr>
<td>Megestrol acetate‡</td>
<td>8-17</td>
<td>12-18</td>
</tr>
<tr>
<td>Third generation aromatase inhibitors§</td>
<td>11-24</td>
<td>18-23</td>
</tr>
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</table>


Patients treated with letrozole 2.5 mg compared with those receiving letrozole 0.5 mg or megestrol acetate. Compared with patients given megestrol, those receiving letrozole 2.5 mg had significantly improved time to treatment failure and response duration. Substantially more patients given megestrol acetate than given letrozole 2.5 mg (29% compared with 19%) experienced serious adverse effects (death, life-threatening events requiring admission to hospital). Weight gain was also more frequent in patients receiving megestrol acetate.
Tamoxifen resistance

Data on tamoxifen resistance developing after 5 years in adjuvant therapies, although preliminary, are consistent with clinical observations of eventual disease progression in all stage-IV breast cancer patients, despite initial responses to tamoxifen. The results are also consistent with experimental evidence of tamoxifen resistance developing in clones exhibiting previous sensitivity to tamoxifen. As with resistance to chemotherapy (Goldie & Coldman 1979), higher rates of mutational events, at multiple levels, are expected to develop at late stages of tamoxifen therapy. Several explanations for tamoxifen resistance have been offered. These include a shift of tamoxifen metabolites from estrogen antagonists to estrogen agonists (Gottardis & Jordan 1988, McGuire et al. 1991, Osborne et al. 1991, Bilimoria et al. 1996, Dowsett et al. 1997), and alterations in interactions between tamoxifen and the estrogen receptor (McGuire et al. 1991, Bilimoria et al. 1996, Dowsett et al. 1997). Thus the originally antiestrogenic response would result in an estrogen-agonistic pathway. Another mechanism of tamoxifen resistance may include the presence of increasing concentrations of estrogen as a result of increased intratumoral aromatase activity.

Regarding the latter mechanism, several laboratories have reported greater aromatase activity in malignant breast tissue compared with the benign parenchyma (Miller & Forrest 1974, Van Landegham et al. 1985, Bulun et al. 1993, Dowsett et al. 1996, Lu et al. 1996, Miller et al. 1997, Blankenstein et al. 1998). This mechanism, of great relevance to breast cancer biology, may provide a part of the explanation for tamoxifen resistance, as increasing tissue estrogen concentrations would prevail over the antiestrogenic impact of tamoxifen. The increasing intratumoral estrogen concentrations occurring during antiestrogen therapy would inevitably support an interactive approach of antiestrogens with aromatase inhibitors.

Randomized studies of aromatase inhibitors and tamoxifen

Stage IV disease. There are in progress at present two randomized trials, one European and one in North America both comparing anastrozole and tamoxifen as first-line agents in the treatment of metastases. Recruitment to the trials has recently reached the targeted number of close to 1000 patients. In addition to response rates, outcome analysis will also include more detailed lipid profile measurements.

Adjuvant setting - the combination. The largest adjuvant trial is the ATAC (anastrozole, tamoxifen combination) study, which involves a multicenter group co-ordinated from the UK undertaking a randomized trial of anastrozole 1 mg compared with tamoxifen and with the combination. The primary objective of this trial is disease-free and overall survival. The secondary objective is collection of information on contralateral breast and uterine cancers and other estrogen-related events, and data on bone and lipid metabolism, and quality of life. To date, close to 7000 patients have been enrolled, with target numbers extended to 8500.

Adjuvant setting - the sequential approach. The sequential approach of aromatase inhibitors following tamoxifen in adjuvant therapy is being tested in a recently activated study that started initially as a Canadian National Cancer Institutes. This was recently extended as an Intergroup trial, with the expected participation of the Eastern Cooperative Oncology Group and South West Oncology Group (SWOG). It is designed as a randomized trial of letrozole 2.5 mg by mouth compared with placebo for stage I-II breast cancer patients who completed 5 years of adjuvant tamoxifen treatment. A similar, four-arm, trial started recently in Europe, with letrozole compared with tamoxifen each for 5 years; compared with letrozole for 2 years followed by tamoxifen for 3 years; compared with tamoxifen for 2 years followed by letrozole for 3 years. Objectives of these trials are to achieve disease-free and overall survival, and to assess the incidence of contralateral primary tumors. The trials will therefore add a valuable wealth of data on whether the addition of new aromatase inhibitors will overcome tamoxifen resistance in adjuvant therapies.

Hormonal prevention of breast cancer

Tamoxifen data on decreased contralateral breast cancer incidence (Breast Cancer Trials Committee 1987, CRC Adjuvant Breast Trial Working Party 1988, Fisher et al. 1989, Formaner et al. 1989. Early Breast Cancer Trialists’ Collaborative Group 1992), reduced cholesterol levels (Rossner & Wallgren 1984, Love et al. 1990) associated with lower cardiovascular morbidity and mortality (McDonald & Stewart 1991, Rutqvist & Mattsson 1993), diminished bone density loss (Love et al. 1988, Turken et al. 1989), led to proposals (Cuzick et al. 1986, Jordan 1990, Love 1990), and later to the initiation in the early 1990s, of tamoxifen breast cancer prevention trials, both in Europe (Powles et al. 1989a) and in North America (Fisher 1992). The UK trial confirmed the feasibility of randomly assigning the trial population of women to tamoxifen or control groups (Powles et al. 1989b). The pilot US trials also confirmed the benefits of tamoxifen in preventing bone loss and achieving reduced cholesterol levels in healthy women (Love et al. 1988, 1990). Recently reported outcome results of the NSABP P-1 study (Fisher et al. 1998b) showed a significant, 49%, reduction in the incidence rate of invasive breast cancer as a result of tamoxifen prophylaxis (relative risk...
(RR)\(=0.51\). Also reduced were the incidence rates of \textit{in vivo} cancers (RR\(=0.50\)). These data are the first to indicate a potential for antiestrogens to prevent the incidence of breast cancer.

The role of aromatase inhibitors in prevention of human breast cancers has not yet been established. They provide, however, an ideal model for therapy in a preventive setting, because of the evidence of increased aromatase activity in the breast parenchyma (Miller & Forrest 1974, Van Landegham \textit{et al.} 1985, Bulun \textit{et al.} 1993, Dowsett \textit{et al.} 1996, Lu \textit{et al.} 1996, Miller \textit{et al.} 1997, Blankenstein \textit{et al.} 1998). These data also support the hypothesis that reduced concentrations of estrogen after treatment with aromatase inhibitors may lead to inhibition of malignant transformation, particularly in the early stages of carcinogenesis.

**Late mortality in breast cancer survivors**

The long-term impact of aromatase inhibitors is particularly relevant as the number of breast cancer survivors is increasing. Thus health issues other than the primary metastatic breast cancer will gain importance in proportion, and will have to be monitored vigorously. With tamoxifen, the interaction of estrogen-agonistic and -antagonistic effects at different organ sites make its overall effect very complex. Recently, its impact on competing all-cause mortality in breast cancer survivors has been reported (Ragaz & Coldman 1998). The analysis showed in tamoxifen-treated patients that, at any age at diagnosis between 50 and 90 years, there will be a more substantial reduction in mortality from the combined avoidance of contralateral breast cancer and cardiac events, despite a moderately increased mortality from uterine cancer and thromboembolic episodes. These benefits are in addition to the well documented reduction in mortality from primary breast cancer. The overall impact of aromatase inhibitors on long-term mortality may also be of great importance, particularly as their use in many new trials will involve women who have already survived their first 5 years of tamoxifen therapy. Thus, in the new studies, as in prevention trials, women of long life expectancy will be treated.

Cause for caution in respect of such approaches is the expectation that, while reduced estrogen concentrations may benefit the breast cancer outcome, they may adversely affect bone and lipid metabolism. The recently initiated adjuvant trials of new aromatase inhibitors will provide some information in this regard, as they will include collection of information on markers of lipid and bone metabolism. Although it is possible that the generalized antiestrogenic effect could affect bone metabolism and cardiovascular status in an adverse way, the expected preferential suppression of aromatase activity in malignant breast clones compared with non-malignant tissues does raise the possibility of a dual antiestrogenic effect of the new inhibitors, more pronounced in the malignant breast parenchyma than in other organs. Indeed, preliminary experimental toxicology data failed to show significant adverse effects of anastrozole or letrozole on either bone or cholesterol metabolism. These important points will have to be confirmed in the clinical setting in new studies.

**Aromatase inhibitors and adjuvant chemotherapy**

Adjuvant chemotherapy remains the mainstay of post-mastectomy systemic therapy. The long-term evaluation of adjuvant chemotherapy trials confirms continuing significant survival benefit of conventionally accepted regimens, with long-term reduction in mortality of 20-30\% (Early Breast Cancer Trialists’ Collaborative Group 1992, Osborne \textit{et al.} 1996). Adjuvant chemotherapy issues of great interest at the present time include: the role of new agents over the accepted cyclophosphamide methotrexate S-FLi (CMF) combinations (taxanes, anthracyclines, etc.); the impact of high-dose chemotherapy regimens requiring stem cell rescue; neoadjuvant (preoperative) chemotherapy, with or without new agents; the integration of biological markers with chemotherapy, etc. These areas are covered by a wide range of current randomized trials. The next several years will probably bring more definitive results in most of them.

Premenopausal patients in whom ovarian function will cease permanently as a result of chemotherapy could become candidates for aromatase hormonal trials, in common with \textit{de novo} postmenopausal women. Measurements of FSH and estrogens in chemotherapy-treated premenopausal patients are at present not performed routinely. Thus the absence of a menstrual cycle and the presence of hot flushes could be important surrogates of menopause, and should probably constitute an important aspect of data collection in new investigative chemotherapy trials. In this regard, a very important issue is that of functional ovarian aromatase rendering aromatase inhibitors ineffective. Also, a question requiring careful evaluation is whether or not patients who became postmenopausal as a result of chemotherapy have a lower response to aromatase inhibitors compared with ‘genuinely’ postmenopausal patients. The answer may depend upon testing, particularly, those cohorts in whom the chemical castration is temporary. Indeed, as a function of patients’ age and the intensity of chemotherapy dosing, the majority of young patients treated with adjuvant chemotherapy will go on to restart full ovarian cycles. In the majority of those patients (younger than 40 years) aromatase inhibitors will probably be less effective than in
older premenopausal women (older than 40-45 years) who, in the majority of cases, will undergo permanent menopause after adjuvant chemotherapy. In this regard, high-dose intensive chemotherapy regimens requiring stem cell rescue may have a potential for a more profound ovarian suppressive effect.

**Aromatase inhibitors in neoadjuvant therapy**

Neoadjuvant (preoperative) therapy has been pioneered over the past 20 years, initially with adjuvant chemotherapy (Ragaz et al. 1991, 1997a Frei et al. 1986, Bonadonna et al. 1991, Mauriac et al. 1991, Powles et al. 1995, Fisher et al. 1998a). There are several concepts justifying the underlying rationale (Frei et al. 1986, Ragaz et al. 1985). Earlier introduction of systemic therapy may reduce the absolute number of resistant mutants (Goldie & Coldman 1979); large tumors can be downstaged, so more conservation is possible (Bonadonna et al. 1991, Dowsett 1998, Fisher et al. 1998a; M Dowsett 1998, personal communication); and surgery may be avoided entirely (Ragaz et al. 1991). Most exciting is the potential for tumors exposed to therapy to provide material ideally suited for assessing markers of tumor biology or therapeutic effects (Makris et al. 1997). The outcomes of several stage I-III neo-adjuvant chemotherapy trials have been reported in the past decade (Mauriac et al. 1991, Powles et al. 1995, Ragaz et al. 1985, Fisher et al. 1998a).

Recently, neoadjuvant studies have been undertaken with new generation aromatase inhibitors. Gazet et al. (1996) reported a 35% response rate to a 3-month course of 4-OHA given as a primary systemic therapy. Dixon et al. (1998) reported pathologically significant responses with an 85% response rate to letrozole in neoadjuvant therapy, compared with a 48% response seen after tamoxifen. The largest test of neoadjuvant therapy with aromatase inhibitors will come from the recently activated UK trial, in which 150 patients will be randomly assigned, as in the ATAC trial, to receive anastrozole or tamoxifen or their combination, all given preoperatively, with biomarkers as the primary end-point (M Dowsett 1998, personal communication).

**Other hormonal developments: SERMs**

Raloxifen represents the new generation of agents - selective estrogen receptor modulators, the SERMs (Clemens et al. 1983, Gottardis & Jordan 1987, Cole et al. 1997, Delmas et al. 1997, Rowley et al. 1997, Sporn et al. 1997, Cummings et al. 1998, Jordan 1998, Jordan et al. 1998). These have, in common with tamoxifen, a preserved antiestrogenic activity against breast cancer and estrogen-agonistic activity against cholesterol and bones; but, in contrast to tamoxifen, they have virtually no estrogenic stimulation of the endometrial tissue, as a result of successful modification of the molecule domain at the level of estrogen receptor-binding ligand responsible for endometrial stimulation (Rowley et al. 1997, Jordan 1998). This represents a major step forward, as the fear of uterine cancer is still a main deterrent against routine use of tamoxifen in preventive or adjuvant therapies. The first large US trial of raloxifen in osteoporosis, with a study population of more than 7700 postmenopausal women, was a randomized study of raloxifen compared with placebo (Delmas et al. 1997, Cummings et al. 1998). Results confirmed not only a substantial prevention of bone loss, but also an impressive reduction of contralateral breast cancer incidence (Cummings et al. 1998, Jordan et al. 1998). These observations make raloxifen a candi-date hormone for a new NSABP prevention trial (the NSABP P-2 study), at present in the final stages of preparation. This randomized trial will assign a high-risk population of women to receive tamoxifen for 5 years or raloxifen for 5 years, with eligibility criteria similar to those for the NSABP P-1 trial.

Additional refined SERMs (the SERM III class) are in the research development stages, some of them as much as tenfold more effective in antiestrogenic activity than raloxifen (Rowley et al. 1997, Sporn et al. 1997). Also, in vivo molecular alterations, as viewed from the crystal structure of the estrogen receptor ligand-binding domain, provide indications for non-crossresistance of raloxifen with tamoxifen (Jordan 1998). Interaction of aromatase inhibitors with new SERMs, either in sequential or combination schedules, may perhaps prove to be even more effective than with tamoxifen, particularly as SERMs have a better effective profile than tamoxifen on tissues other than breast cancer. SERMs may, therefore, compensate more effectively for the lack of estrogen agonist activity of aromatase inhibitors on lipid and bone metabolism. As with tamoxifen, aromatase inhibitors will have to be tested in conjunction with SERMs, in order to prove this important point.

**Other hormonal developments: the 'pure antiestrogens'**

Faslodex, the long-acting ICI-182 782, is one of the first agents of the class of “pure antiestrogens", the most potent antiestrogens developed (Bowler et al. 1989, DeFriend et al. 1994, Howell et al. 1995, Osborne et al. 1995). In vivo and experimental studies with ICI-182 782 have shown that, upon binding to the estrogen receptor, a profound interaction with estrogen receptor protein takes place, resulting in a substantial biochemical ablation of the estrogen receptor protein (Bowler et al. 1989, Osborne et al. 1995). Thus no binding of estrogen is possible.
Because of its pronounced degradation in the human gastrointestinal tract, faslodex has to be given as an i.m. injection, once a month. Several phase II studies showed 20-30% response rates in patients who failed to respond to tamoxifen, with response durations of 12-24 months (Howell et al. 1995). A recently started Intergroup trial is randomizing faslodex and anastrozole as second-line therapies in stage IV patients who failed to respond to tamoxifen (Faslodex Intergroup Trial I: Faslodex vs Anastrozole, 1997 - K Osborne, personal communication). A new Intergroup trial has also started recently, randomizing faslodex and tamoxifen as first-line therapies for metastatic disease (Faslodex Inter-group Trial II: Faslodex vs Tamoxifen, 1998 - K Osborne, personal communication). A new pure antiestrogen, the Scherring product, 57050 (SP 57050), has been developed recently; it can be taken orally as a daily tablet. The Breast Cancer International Research Group (BCIRG) recently started a study of SP 57050 in comparison with anastrozole, as first-line therapy in stage IV disease (BCIRG Intergroup Trial: SP 57050 vs Anastrozole, 1998 - J M Nabholtz, personal communication).

Taking into account experimental observations, the substantial degradation of estrogen receptor by pure antiestrogens may predict little additional benefit of further reducing estrogen concentrations by means of aromatase inhibitors. This would be the case unless resistance to the pure antiestrogens were to develop. As the formation of resistance to any drug is a realistic possibility, the potential for interaction of pure anti-estrogens with aromatase therapy will also require consideration and testing.

**Biological aspects of breast cancer therapy**

From the molecular biology arena, of great interest is the increasing clinical impact of mutated marker genes, including BRCA 1/2 (Hall et al. 1990, Miki et al. 1994, Easton et al. 1993, Weber & Garber 1996) and ataxia telangiectasia (Swift et al. 1991), in determining breast cancer susceptibility. This is particularly relevant in familial breast cancer (Weber & Garber 1996). A need to refine clinical management in individual cases on the basis on these markers, interacting with family history and other risk factors, has resulted in the establishment of genetic units affiliated with many cancer centers. These coordinate the management and counseling of affected individuals or their families with respect to issues such as prophylactic mastectomy, screening mammography at earlier age, participation in chemoprevention initiatives, and so on.

Other biological markers, such as a mutated HER/NEU gene and its expressed erbB-2 protein, are showing great clinical relevance. Mutated erbB-2 has recently been shown to predict response to chemotherapy dose intensification (Thor et al. 1998), absence of survival benefit to tamoxifen (Bianco et al. 1998), or selected response to specific chemotherapeutic agents such as topoisomerase inhibitors (Paik et al. 1998, Ravdin et al. 1998). Thus there is more evidence for association of erb-B2 with disease outcome and therapy selection, with evidence sufficiently compelling, according to some researchers, to suggest that erb-B2 should be available in the routine management of breast cancer (Bianco et al. 1998, Clark 1998, Paik et al. 1998, Ravdin et al. 1998, Thor et al. 1998).

Antibody to HER/NEU receptor, Herceptin, has recently become available. The first clinical phase I-II data in stage IV breast cancer indicate measurable response rates either to Herceptin alone (Cobleigh et al. 1998) or to Herceptin with a taxol-doxorubicin combination (Slamon et al. 1998).

Biphosphonates have shown clinical relevance in breast cancer. Both clodronate daily by mouth for 2 years and pamidronate i.v. monthly for 1 year have been shown to reduce significantly the incidence of bone pains and fractures associated with breast cancer skeletal metastases (Paterson et al. 1993, Hortobagyi et al. 1996). A UK-Canadian trial has shown clodronate to reduce skeletal events when given in adjuvant therapy (Powles et al. 1998), and a recent German study showed that not only skeletal, but also visceral metastases (lung, liver) were reduced by clodronate (Diel et al. 1998). Thus a modulation of the host tissue (bone) affecting subsequent metastases, if confirmed, would support a previously proposed analogy, for cancer biology, with a soil-seed interaction. Reduction of visceral metastases by adjuvant clodronate also provides provocative data on bones as a main source of secondary dissemination of subclinical, microscopic breast cancer clonogenic cells. Aromatase inhibitors, known from earlier studies with amino-glutethimide selectively to improve bone metastases (Lipton et al. 1982), will probably interact with biphosphonates. As with other hormones, such interaction will require both laboratory and clinical testing.

In some aspects, aromatase inhibition would fulfill the criteria of biological therapy, as an altered locoregional estrogenic milieu resulting from increased aromatase activity can be defined as one of the carcinogenic events. Thus, suppression of aromatase activity could be considered a biologically target-directed approach.

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