Introduction

The beginnings of endocrine therapy for breast cancer can be traced to British surgeon George Beatson. In 1896, he described a young woman with lo cally recurrent breast cancer who responded to oophorectomy. Today, several endocrine therapies are available, including selective estrogen receptor modulators (tamoxifen and others), aromatase inhibitors, progestins, androgens, and LHRH agonists. Approximately 30% of patients with metastatic disease respond to endocrine therapy, with the average duration of response lasting about six months to one year. While the overall response rate is higher with chemotherapy than with endocrine therapy (about 70% to 40%), the duration of response, at about nine months, is somewhat shorter for chemotherapy-treated patients. Clinical criteria predicting a greater likelihood of response to endocrine therapy are positive estrogen receptor (ER) and/or progesterone receptor (PR) status, soft-tissue metastases, longer disease-free interval, and increasing age.

First-Line Treatment: Endocrine Therapy vs Chemotherapy

As the proper role of endocrine therapy is considered, the question arises: Should a patient with metastatic disease who is not critically ill receive endocrine therapy as first-line systemic treatment or chemotherapy? Based on the results of two randomized clinical trials, women with metastatic breast cancer, especially those who are ER/PR positive, should receive a trial of endocrine therapy first. The exception to this is the patient with extensive and rapidly progressive visceral disease.

This issue was examined in an Australian study involving 339 postmenopausal women with metastatic breast cancer. Hormone receptor status was unknown in 75% of the patients. Patients were randomized to receive either tamoxifen, tamoxifen plus concurrent chemotherapy with cyclophosphamide and doxorubicin, or chemotherapy alone. The response rate for those receiving tamoxifen (22%) was inferior to those receiving chemotherapy alone (45%) or tamoxifen plus chemotherapy (51%), but overall survival was virtually identical among the three arms. Moreover, 35% of the tamoxifen-treated patients responded to chemotherapy as second-line therapy. In a similar trial comparing combination chemotherapy (cyclophosphamide, methotrexate, and fluorouracil) vs tamoxifen in older patients, the response rates, duration of response, and survival among endocrine and chemotherapy-treated patients were virtually identical regardless of estrogen receptor status.

Important to the use of endocrine therapy in metastatic breast cancer is the observation that a patient’s response to first-line therapy is predictive of response to second- and third-line treatment. Unless patients have rapidly progressive disease, the sequential use of endocrine therapies is an excellent strategy to minimize toxicity of treatment while maintaining a high quality of life.

Endocrine Therapy

Among endocrine therapies available today, tamoxifen remains superior, with its efficacy demonstrated in both premenopausal and postmenopausal patients in virtually all comparative trials. Numerous efforts are underway to develop not only new selective estrogen receptor modulators (SERMs) with better biologic profiles, but also pure antiestrogens. New aromatase inhibitors have displaced progestins as second-line therapy in postmenopausal patients and are currently being evaluated in the adjuvant setting. Also, trials are currently underway with pure antiestrogens and new aromatase inhibitors.

LHRH agonists are effective in premenopausal patients with metastatic breast cancer and are being evaluated in the adjuvant setting. Furthermore, limited data suggest that the addition of an LHRH agonist to tamoxifen may be associated with superior response rates compared to tamoxifen alone. A small, randomized trial also suggested a superior response rate to tamoxifen and buserelin compared with tamoxifen alone. Jonat and colleagues compared the LHRH agonist goserelin with goserelin and tamoxifen. While response rates and survival were similar, there was a slight but significant improvement in time to progression favoring the combination regimen. Several European trials are comparing tamoxifen and LHRH agonists and tamoxifen in combination with LHRH agonists as adjuvant therapy in ER-positive premenopausal patients with early-stage breast cancer.

The Ideal SERM

The quest for the ideal SERM continues. Researchers have a precise target in mind (Table 1). The ideal SERM should have antiestrogen properties on the breast and the uterus and an estrogenic effect on the brain (to prevent hot flashes). It should have an estrogen effect on the liver (to lower cholesterol synthesis) and on bone (to maintain calcium). Also, it should exert no effect on the coagulation system. To date, SERMs other than tamoxifen have not shown higher response rates, although some (eg, raloxifene) may have lesser estrogenic effects on the uterus. Currently, tamoxifen is the SERM of choice for use in prevention and in the adjuvant setting, and it remains the benchmark for comparison with other agents.

<table>
<thead>
<tr>
<th>Table 1.— The Ideal SERM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tamoxifen</strong></td>
</tr>
<tr>
<td>Breast</td>
</tr>
<tr>
<td>Uterus</td>
</tr>
<tr>
<td>Brain</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Bone</td>
</tr>
<tr>
<td>Deep Venous Thrombosis</td>
</tr>
</tbody>
</table>

E = estrogen
As unique compounds that bind to estrogen receptors and prevent dimerization of receptors, pure antiestrogens are absolute antagonists as they render receptors completely nonfunctional. In an early trial conducted by Howell and colleagues in tamoxifen-resistant patients, ICI 102,780 (Faslodex) was administered to 19 postmenopausal tamoxifen-resistant women with advanced breast cancer. Ten patients had relapsed on adjuvant tamoxifen, and nine had received tamoxifen for metastases. Partial responses of 3 to 20 months’ duration were seen in seven patients (37%), and six patients (32%) had stable disease with a duration of 9 to 23 or more months. No hot flashes were noted. Although further studies may find drawbacks (eg, loss of potentially beneficial effects on bone and lipids) to this type of agent, they have great promise because of the unique mechanism of action. Clinical trials are underway comparing ICI 102,780 with aromatase inhibitors in women with metastatic breast cancer.

Aromatase Inhibitors

Aromatase (estrogen synthase), an enzyme present in fat, liver, breast tissue, and perhaps breast cancer cells, converts androstenedione to estrone — E1 (Fig 1). The new aromatase inhibitors cause little or no inhibition of glucocorticoid synthesis (unlike ketoconazole and aminoglutethimide), and thus there is no risk of hypoadrenalism and potential need for supplementary glucocorticoids.10

Fig 1. — Aromatase (estrogen synthetase) converts androstenedione to estrone.

There are two types of aromatase inhibitors. Type I are steroidal compounds and include 4-hydroxy-androstenedione, formestane, and exemestane. Steroidal aromatase inhibitors are noncompetitive inhibitors that interfere with the cytochrome P450 site on the enzyme to bring about irreversible inhibition. Type II aromatase inhibitors are non steroidal competitive inhibitors of the flavoprotein site on the aromatase enzyme. They include the triazole analogs anastrozole (Arimidex), letrozole (Femara), and vorozole. Within several days after administration of these agents to postmenopausal women, serum estradiol levels are suppressed to extremely low levels.11 Aromatase inhibitors are not very effective in premenopausal women because of the high level of estradiol synthesis in the ovaries.

Anastrozole vs Megestrol Acetate

One large trial compared anastrozole with megestrol acetate in postmenopausal women with advanced breast cancer after tamoxifen failure (Table 2).12 Although the results showed only a 12% incidence of complete and partial responses, stable disease lasting six months or longer was achieved in almost 30% of patients. The two-year survival was higher for the anastrozole-treated patients, even though the median time to progression was similar at about five months for anastrozole and megestrol. There is a clinically significant value to stable disease longer than 24 weeks because if tumors do not progress over a period of approximately six months, the patients can be expected to live as long as responders.

<table>
<thead>
<tr>
<th>Table 2. — Anastrozole vs Megestrol Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anastrozole 1 mg/day</strong></td>
</tr>
<tr>
<td>Number of Patients</td>
</tr>
<tr>
<td>Median Time to Progression (mos)</td>
</tr>
<tr>
<td>Complete or Partial Tumor Response</td>
</tr>
<tr>
<td>Stable Disease &gt; 24 wks</td>
</tr>
<tr>
<td>Estimated 2-yr Survival</td>
</tr>
<tr>
<td>Median Survival (mos)</td>
</tr>
</tbody>
</table>

Data from Buzdar et al.15

Letrozole vs Megestrol Acetate

Letrozole (Femara) has also been compared to megestrol acetate in a randomized clinical trial as second-line hormone therapy in patients with metastatic disease. In one study of 551 patients,13 letrozole (2.5 mg) not only produced a 24% overall response vs a 16% response with megestrol acetate, but also showed a trend for a longer time to progression. Overall survival was similar. Letrozole was also significantly better tolerated than megestrol.

Endocrine Therapy for Metastatic Breast Cancer

Treatment Sequence for Premenopausal Women

Tamoxifen, LHRH agonists, and oophorectomy have displayed similar response rates when used as first-line therapy for premenopausal patients with metastatic disease. Upon disease progression, patients who respond to one of these modalities may respond to another, such as tamoxifen after oophorectomy (Fig 2). For patients who have responded to tamoxifen, oophorectomy, and/or LHRH agonists and for those with slowly metastatic disease, progestins and aromatase inhibitors may be helpful in a small percentage of patients. Androgens such as fluoxymesterone may also be effective. Patients who respond to endocrine therapy or who have periods of stable disease exceeding four to six months should be observed for possible withdrawal responses at the time of disease progression.
Treatment Sequence for Postmenopausal Women

A suggested sequence for the use of endocrine agents in postmenopausal women is shown in Fig 2. Tamoxifen should be the first-line agent of choice in this setting. For women receiving tamoxifen in the adjuvant setting who develop metastatic disease, tamoxifen should again be considered if the duration from completion of tamoxifen to the development of metastases is longer than one year. For second-line therapy, the aromatase inhibitors have moved ahead of megestrol acetate based on their slightly better efficacy and more favorable toxicity profile. Aromatase inhibitors avoid the weight gain associated with progestins. There is still a role for progestins and estrogens as third- and fourth-line therapies, respectively, especially for the few patients who have responded to prior endocrine therapies and for those with slowly metastatic disease. Glucocorticoids can also be considered for these patients. Since all therapy in patients with metastatic breast cancer is palliative, continuing endocrine therapy for as long as possible — especially in patients with minimal or no symptoms and slowly progressive disease — is a good strategy.

References


Discussion

Dr Perez: Over the years, we have seen modest response rates with most hormonal agents in virtually every setting. More research is needed regarding hormonal therapy resistance.

Dr Muss: In addition to ER and PR, factors that increase the likelihood of a response to endocrine therapy include a long disease-free interval, fewer number of metastatic sites, better performance status, and older age. This should be the era to look for new molecular
markers that predict response, but such markers have not yet been identified.

Dr Sledge: I agree entirely. I think it’s fascinating that until two years ago, we blithely assumed that there was only one estrogen receptor. I haven’t seen any data yet to say that measuring ER-beta as opposed to ER-alpha makes any difference in terms of hormonal response. It would be interesting to know because tamoxifen and receptors were the first cases of targeted therapies in breast cancer or in any cancer. It would be wonderful if we could target them even better.

Dr O’Shaughnessy: The randomized data have suggested improved response rates with oophorectomy first-line for premenopausal women with metastatic disease. Am I correct? Also, was there a survival advantage by adding LHRH antagonist to tamoxifen? I have been using the combination based on those data, but I’m curious to know what you’ve been doing.

Dr Muss: Combined endocrine therapy with an LHRH agonist and tamoxifen may be better than an LHRH agonist or tamoxifen alone, but data currently available are far from compelling. I think more data from clinical trials are needed. Currently, I still recommend single-agent treatment. I hope the adjuvant studies being conducted in Europe will resolve some of these issues.

Dr O’Shaughnessy: It is not uncommon to see some sort of a thrombotic event with hormones. I thought that the aromatase inhibitors had a lower incidence of thromboembolic events. What is your impression?

Dr Muss: My impression is that this is true.

Dr Horton: What would you do for a patient with advanced disease who is both ER-positive and strongly HER-2-positive and is clinically a suitable candidate for hormone therapy?

Dr Muss: I’d treat with hormone therapy. The relationship between HER-2 expression and response to endocrine therapy in patients with metastatic disease is controversial. Some differences relate to methodology for measuring HER-2. In my opinion, HER-2 should not be used for treatment selection in these patients.

Our experience in the CALGB with a large group of node-positive patients showed no interaction of tamoxifen and HER-2 in the adjuvant setting. Tamoxifen-treated patients had similar and superior outcomes when compared with patients not receiving tamoxifen, regardless of HER-2 expression.

Dr Horton: Are there any indications to use hormones and cytotoxic therapy together?

Dr Muss: Historically, several clinical trials compared combinations of endocrine therapy and chemotherapy with endocrine therapy alone. Although several showed higher response rates for combined therapy, none showed any convincing survival advantage. I treat with endocrine therapy first and reserve chemotherapy for patients with tumors that have become refractory to endocrine treatment. The exception might be a patient with rapidly progressing visceral disease in whom another tumor doubling or less would be catastrophic — such as someone with shortness of breath and lymphangitic spread.

Dr Sledge: Every physician has a hierarchy of therapeutic goals. We would all like to prolong survival, but beyond that, quality of life has to be placed very high. Targeted endocrine therapies are relatively nontoxic regimens. If they can put the patient into remission for a prolonged period of time with minimal toxicity, it seems to me that there is little advantage to adding chemotherapy to that.

The author is a member of the Speakers Bureau for AstraZeneca, PLC.