In addition to ovarian ablation by means of surgery or irradiation, a wide variety of endocrine agents are now available for the management of breast cancer, in both the metastatic and adjuvant settings. Currently available

**Introduction**

Endocrine approaches to the treatment of metastatic breast cancer were first suggested in the late 1800s by Beatson.[1] At about the same time, Schinzinger[2] suggested the use of irradiation to the ovaries as perhaps the first form of adjuvant systemic therapy. Surgical removal of the ovaries and/or ovarian ablation by irradiation arose from these original ideas and became standard therapy in the 1950s and 60s both for metastatic breast cancer and in the adjuvant setting. As the human endocrine system became better understood, it seemed clear that these treatments worked by reducing estrogen levels. It was also observed that women who underwent surgical ovarian removal without hormone replacement were at a greatly reduced risk of developing breast cancer.[3] This was perhaps the first demonstration of endocrine prevention.

During the 1950s and 60s, a variety of other endocrine approaches were developed, but these were mainly surgical. They included the use of adrenalectomy and hypophysectomy as second-line endocrine therapies for premenopausal women who initially had positive responses to ovarian ablation. Unfortunately, these procedures were accompanied by both immediate complications and the long-term requirement for various types of endocrine replacement. Nevertheless, these ablative therapies were used with considerable success into the 1970s.

With the development of modern endocrine agents, including the antiestrogens, progestational agents, and first, second-, and third-generation aromatase inhibitors, a wide variety of more palatable endocrine approaches are now available. These newer endocrine therapies continue to supplement and rival chemotherapeutic and radiation approaches in the management of breast cancer.

**Treatment of Metastatic Disease**

The most appropriate hormonal therapy for a patient with metastatic breast cancer depends, in large part, on the patient’s menopausal status.

**Premenopausal Women**

As mentioned above, the role of ovarian ablation as a treatment for premenopausal women with metastatic disease has long been appreciated. First introduced around the turn of the 20th century,[1,2] this therapy was used, without any ability to select patients, for many decades. With the discovery of the estrogen receptor by Jensen et al[4] in the 1950s, it became apparent that women who have measurable estrogen receptors and, subsequently, progesterone receptors in their tumors were more likely to respond to endocrine maneuvers than were those who have only one or neither receptor measurable.[5] Levels of estrogen and progesterone receptors were also found to predict response to hormonal therapy.[5]

About 30% of women with tumors positive for either estrogen or progesterone receptors and about 60% of women with tumors positive for both receptors will respond to endocrine maneuvers. Women with higher levels of estrogen and/or progesterone receptors are more likely to respond than are those with lower but still positive levels.[5] The use of ovarian ablation remained limited in the 1960s, 70s, and early 80s however, by the requirement for either a course of pelvic irradiation or a major surgical procedure.

A further development during the 1990s was the widespread availability of ovarian ablation by laparoscopic means. This relatively simple procedure can be carried out in the outpatient setting in most women requiring surgical ovarian ablation, and has made ovarian ablation a more acceptable
therapy. Early in the development of tamoxifen (Nolvadex), small, comparative studies\[6-8\] showed that tamoxifen was equally effective to ovarian ablation in the metastatic setting. A subsequent meta-analysis, although still containing a relatively small number of patients randomized between these two treatments, further clarified the approximate equivalence of these two therapies.\[9\] Because tamoxifen could be administered orally, had few side effects, and did not result in permanent ovarian ablation, it became the drug of choice in many situations for the treatment of premenopausal women with metastatic disease.

In the 1970s, the luteinizing hormone-releasing hormone (LHRH) analog were developed. These agents, particularly goserelin (Zoladex), were explored in metastatic breast cancer, and numerous phase II studies showed activity in this setting. Subsequently, the results of a large randomized study confirmed the equivalence of goserelin to ovarian ablation.\[10\]

More recently, four small studies comparing tamoxifen plus an LHRH analog to an LHRH analog alone have suggested that the combination may be superior in terms of time to progression and overall survival.\[11\] Once again, meta-analysis of these four trials has been helpful in suggesting that there may be a benefit to the combination in comparison to an LHRH analog alone.\[11\] Because tamoxifen is generally used as first-line therapy in this setting, however, the more germane question remains whether tamoxifen plus an LHRH analog is superior to tamoxifen alone. Randomized trials to answer this question should be considered.

**Treatment Recommendations**

In the meantime, it seems clear that premenopausal women who are estrogen receptor and progesterone receptor positive and/or have suitable clinical characteristics (eg, long disease-free interval, soft-tissue and/or bone involvement, pleural effusion, slow pace of disease) remain candidates for endocrine approaches to the treatment of breast cancer. These women can receive either tamoxifen or ovarian ablation by medical, surgical, or radiotherapeutic means as first-line endocrine therapy. The combination of an LHRH analog and tamoxifen could also be considered for first-line treatment.

For women whose disease responds to initial ovarian ablation but subsequently progresses, tamoxifen should be considered as second-line therapy. For women who begin therapy with tamoxifen, ovarian ablation by medical, surgical, or radiotherapeutic means should be considered as a second-line treatment.

It should be remembered that such drugs as the aromastase inhibitors and the progestational agents have not been shown to be effective in women who are still premenopausal. Thus, some form of ovarian ablation should precede the use of these drugs.

**Postmenopausal Women**

Diethylstilbestrol (DES) was once considered the first-line treatment for all postmenopausal women. With the advent of tamoxifen, however, this much less toxic drug was quickly adopted, perhaps even before the results of randomized trials showing its equivalence were available.\[12\]

Until a few years ago, second-line therapy was probably best delivered by medroxyprogesterone acetate or megestrol acetate (Megace), both of which have been shown to be equivalent to tamoxifen in a variety of randomized clinical trials. However, these progestational agents have an unpleasant side effect profile that includes dyspnea, weight gain, and an increased risk of deep-vein thrombosis and pulmonary emboli.

Over 15 years ago, aminoglutethimide (Cytadren), the prototype of the aromatase inhibitors, became available. In postmenopausal women, virtually all estrogen is produced by aromatase, an enzyme found in brain, muscle, and peripheral fat that converts androgenic hormones produced by the female adrenal gland to estrogens.

Unfortunately, aminoglutethimide was nonspecific, in that it also blocked 11-, 17-, and 21-hydroxylation in the adrenal pathway of steroidogenesis, resulting in reduced production of the mineralocorticoids and glucocorticoids required for life. Thus, aminogluthemide, in daily doses higher than 500 mg, required concurrent hydrocortisone replacement. Aminoglutethimide tended to cause drowsiness, and maculopapular rashes were also common side effects of this agent. The accompanying cortisone had its own set of side effects.

The development of the second-generation aromatase inhibitors, such as formestane (Lentaron), was not terribly helpful, since these were injectable and thus harder to use. Now, however, a wide variety of third-generation aromatase inhibitors, including anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin), have been developed. Each of these drugs has been compared against aminogluthethimide or megestrol acetate in randomized clinical studies.\[13-15\]

All three third-generation aromatase inhibitors have been shown to be superior to megestrol acetate to some degree. Randomized trials of anastrazole have shown improved overall survival.\[15\] while...
randomized trials of letrozole have shown improved time to treatment failure and improved overall survival in comparison to megestrol acetate.[16] Similarly, randomized trials comparing exemestane to megestrol acetate have shown improvements in time to treatment failure, time to progression, and overall survival.[17] In addition, comparisons of letrozole to aminoglutethimide (500 mg) used without hydrocortisone have demonstrated the superiority of the third-generation aromatase inhibitor.[18]

Two trials comparing anastrozole to tamoxifen as first-line therapy for metastatic disease were presented at the 1999 European Cancer Conference (ECCO). One large European study randomized over 650 women to receive either tamoxifen or anastrozole.[19] This study showed almost identical response rates, time to treatment failure, and time to progression for the two drugs. However, less than half of the patients were known to be estrogen receptor positive; estrogen receptor status in the remaining patients was unknown. A similarly designed North American study of about 350 women randomized to tamoxifen or anastrozole, of whom about 90% were positive for estrogen or progesterone receptors, showed a statistically significant benefit, with respect to both time to treatment failure and time to progression, in favor of anastrozole.[20]

The somewhat different results of these two trials seem problematic, and further examination of the data is underway. These preliminary results suggest, however, that this particular aromatase inhibitor may be at least equivalent, if not superior to, tamoxifen in the first-line setting. Further follow-up will be required to confirm these results and to assess survival. Certainly, these data have generated great interest in the upcoming results of a randomized study in which anastrozole (A) is being compared to tamoxifen (T) and to the combination of the two drugs (AT) as adjuvant therapy for receptor positive or unknown postmenopausal women (the so-called ATAC trial).

**Treatment Recommendations** Based on currently available data, postmenopausal women with metastatic disease should be treated first with tamoxifen, followed by a second-generation aromatase inhibitor (anastrozole, letrozole, or exemestane) and then, probably, by megestrol acetate. Drugs with a more problematic side effect profile, such as fluoxymesterone and danazol, can be reserved for fourth-line therapy when required. The rapid development of the aromatase inhibitors and the suggestion that at least one of them, anastrozole, may be equivalent to if not better than tamoxifen in the first-line metastatic setting, suggest that the sequence of hormonal therapies may change over the next few years as more data become available.

**Adjuvant Endocrine Therapy**

Adjuvant endocrine therapy is important in both the premenopausal and postmenopausal setting. **Premenopausal Women**

Adjuvant ovarian ablation was used for many years and was considered to be helpful, but no randomized trials had yet been conducted. Then, in the 1960s and 1970s, a series of small, randomized trials comparing irradiation of the ovaries vs no systemic treatment and surgical ovarian ablation vs no surgical ablation were conducted. These studies initially compared ovarian ablation to no systemic treatment (Table 1). In subsequent trials, however, patients were randomized to receive chemotherapy with or without additional ovarian ablation (Table 2).

Prior to the first Early Breast Cancer Trialists' Collaborative Group overview (also known as the Oxford overview) in 1984,[21,21a,22] it was generally felt that these trials showed little or no beneficial effect of ovarian ablation. Consequently, ovarian ablation came to be thought of as an ineffective, outmoded breast cancer therapy. When the meta-analytic techniques used in the Oxford overview were applied to these small trials, however, it became apparent that ovarian ablation was associated with a positive effect of reasonable magnitude on both disease-free and overall survival in premenopausal women (Figure 1). The effect persisted for node-positive and node-negative groups and remained significant for the subgroup of trials in which women were randomized to receive ovarian ablation alone vs no systemic therapy.

Perhaps because of an already positive effect of chemotherapy and some degree of medical ablation from chemotherapy in the premenopausal group, however, the studies of ovarian ablation plus chemotherapy vs the same chemotherapy used alone showed only a trend toward a positive effect. In one trial comparing premenopausal node-positive and node-negative women randomized to receive intravenous CMF (cyclophosphamide, methotrexate, and fluorouracil), three times weekly for eight cycles, or ovarian ablation, women with estrogen receptor levels > 100 fmol/mg had better disease-free and overall survival with ovarian ablation, while those with estrogen receptor levels < 100 fmol/mg fared better with CMF therapy.[23]

Although this CMF regimen is perhaps not as dose-intensive and, therefore, probably not as effective...
as the standard Bonnadonna CMF regimen (ie, cyclophosphamide [100 mg/m²] on days 1 to 14 and methotrexate [40 mg/m²] and fluorouracil [600 mg/m²], each given on days 1 and 8 intravenously), the study does suggest that ovarian ablation may be as or more effective than some types of chemotherapy in women with high estrogen receptor levels. Few other similarly designed studies were performed until recently.

The next endocrine approach studied in premenopausal women was antiestrogens, particularly tamoxifen. After it was initially explored in metastatic disease in postmenopausal women,[24] tamoxifen was also shown to be effective in the metastatic setting in premenopausal women.[25] It was then tested as adjuvant therapy, first in postmenopausal and then in premenopausal women. Early studies, such as those of the National Surgical Adjuvant Breast and Bowel Project (NSABP)[26] demonstrated the efficacy of tamoxifen when added to chemotherapy in postmenopausal women, particularly if they were estrogen and/or progesterone receptor positive. Subsequent studies using tamoxifen alone vs no systemic therapy (eg, the NSABP B-14 study)[27] showed that tamoxifen produced positive effects on disease-free and overall survival that were similar in magnitude to those of chemotherapy in this setting.

Once again, the first Early Breast Cancer Trialists' Collaborative Group overview[28] showed strong, consistent improvements in women receiving tamoxifen. The early overview analyses included relatively small numbers of premenopausal women randomized to trials of tamoxifen, however, and most trials studied 1 to 2 years of therapy. The results of subsequent trials using 5 years of tamoxifen have clarified the magnitude of benefit afforded by tamoxifen. In the most recent Oxford overview publication focusing on tamoxifen,[29] it was abundantly clear that premenopausal women randomized to receive 5 years of tamoxifen enjoyed substantial disease-free and overall survival benefits (Figure 2), as compared with those randomized to no tamoxifen. Most of the women selected for these later trials were estrogen and/or progesterone receptor positive, which probably also increased the magnitude of the effect seen with tamoxifen. Within the premenopausal group, however, there are still very limited data concerning women randomized to receive chemotherapy alone or chemotherapy plus tamoxifen. In fact, only 205 such women (of whom only 177 were estrogen receptor positive) were included in the most recent Oxford overview.[Peto R, personal communication, 1999] In this subgroup, there is also a trend toward improvement in overall survival and a marginally significant improvement in disease-free survival. However, because of the relatively small number of women studied, the effects in this subgroup are less certain.

At least three trials in which premenopausal women were randomized to receive chemotherapy or chemotherapy followed by tamoxifen are currently ongoing or have recently been completed. Hopefully, the results of these studies will be available within the next few years, perhaps as part of the planned year 2000 Oxford overview.[Castiglione M, personal communication, 1999; Piccart M, personal communication, 1999; Bramwell V, personal communication, NCIC CTG trial MA 12, 1999] The results of these studies will shed more light on whether the use of tamoxifen following chemotherapy is as effective as the use of tamoxifen alone in premenopausal women. Despite the lack of randomized trial data, it is common current practice in many parts of the world, certainly in the United States, to follow chemotherapy with tamoxifen in premenopausal women who are estrogen or progesterone receptor positive.

The development of the LHRH analogs has resurrected interest in the use of ovarian ablation in premenopausal women. One relatively large phase III trial showed the LHRH analogs to be as effective as ovarian ablation in the treatment of metastatic breast cancer.[30] Various LHRH analogs, particularly goserelin, are currently being tested in the adjuvant setting. These studies are comparing goserelin, tamoxifen, or goserelin plus tamoxifen to chemotherapy in the premenopausal setting or are adding goserelin, tamoxifen, or goserelin plus tamoxifen to chemotherapy in the same group of women.

Two trials are of particular interest: A trial by Jakesz et al[31] comparing goserelin plus tamoxifen to CMF chemotherapy suggests that, in estrogen receptor positive women, the former therapy may be superior. Another trial by Rutqvist[32] shows that goserelin, with or without chemotherapy or tamoxifen, provides significant benefit in premenopausal women.

In addition, preliminary results of another very interesting study from the Eastern Cooperative Oncology Group (ECOG) were presented by Nancy Davidson at the 1999 American Society of Oncology (ASCO) meeting.[33] This study, which compared CAF (cyclophosphamide, Adriamycin, and fluorouracil) to CAF plus goserelin or CAF plus goserelin and tamoxifen in premenopausal node-positive women, showed that the addition of goserelin or goserelin plus tamoxifen to chemotherapy resulted in significantly better disease-free survival and a trend toward better overall...
survival, as compared with chemotherapy alone. The addition of tamoxifen to CAF plus goserelin showed only a trend toward an improvement in either relapse-free or overall survival. A preliminary, hypothesis-generating analysis presented by Dr. Davidson, however, suggested that the addition of goserelin was more effective in younger women and/or women who did not become menopausal as a result of chemotherapy, while the addition of tamoxifen seemed more effective in older women and/or in women who became menopausal as a result of chemotherapy. This hypothesis remains to be explored further and substantiated in prospective, randomized trials.

Numerous other studies examining the use of LHRH analogs as adjuvant therapy in premenopausal women, either in direct comparison to or added to combination chemotherapy, are currently underway (Table 3). The results of many of these studies will be available for the 2000 Oxford overview and will shed considerable further light on this situation. These larger and, therefore, more highly powered studies of medical ovarian ablation will add considerably to current knowledge about the role of surgical and irradiation ablation in the adjuvant therapy of premenopausal women.

Treatment Recommendations

In the meantime, however, combination chemotherapy remains a standard adjuvant therapy for premenopausal women. With the development of second- and third-generation combinations, such as CEF (cyclophosphamide, epirubicin, and fluorouracil), which seems to be superior to the standard Bonadonna CMF regimen,[34] and AC (Adriamycin and cyclophosphamide)/Taxol, which appears to be better than AC alone,[35] it is unclear what final conclusions should be drawn from studies that compare first-generation chemotherapy to any type of ovarian ablation.

Thus, the optimal adjuvant therapy for premenopausal women remains a subject for further study. It is clear, however, that both ovarian ablation and tamoxifen represent effective adjuvant treatment options for premenopausal women.

Postmenopausal Women

In the adjuvant setting, early results with combination chemotherapy regimens in postmenopausal women were encouraging,[36,37] but subsequent follow-up suggested that these regimens were most effective in premenopausal women. In the late 1970s, a number of trials were initiated in which women were randomized to receive tamoxifen for 1 or 2 years vs no systemic therapy. Early results of these trials demonstrated that tamoxifen prolonged recurrence-free survival,[38-40] but only a few trials suggested that it afforded an overall survival benefit.[41]

Once again, the initial Oxford overview analysis made it clear that tamoxifen does prolong overall survival, particularly in postmenopausal women and more dramatically in those who are estrogen receptor positive.[28] Subsequent trials of 5 years of tamoxifen therapy have demonstrated even more dramatic benefits.[29] The results of at least three trials that directly compared 2 vs 5 years of tamoxifen are now available; all three trials suggest that tamoxifen therapy for 5 years is the superior approach.[42-44]

Thus, tamoxifen has become the mainstay of adjuvant treatment in postmenopausal women, at least in those whose tumors are estrogen and/or progesterone receptor positive. The effects of tamoxifen seem to be proportionately similar in node-negative and node-positive women (Figure 2) and persist beyond the 5-year period for which the drug is given.

Of course, tamoxifen therapy has both short- and long-term side effects. These consist mainly of hot flashes, vaginal discharge and irritation over the short term, as well as a two- to threefold increased risk of endometrial cancer (this risk increases with the duration of tamoxifen therapy) and an increased risk of deep-vein thrombosis and pulmonary emboli. With the establishment of tamoxifen as the standard therapy in this setting, a number of studies have examined the role of chemotherapy added to tamoxifen. It seems clear that both CMF-containing regimens, given in appropriate schedules,[45] and anthracycline-containing regimens, such as AC and FAC, at least add to disease-free survival[46,47] and probably to overall survival[46] in this setting.

Recently, third-generation aromatase inhibitors, such as anastrozole, have been shown to be equivalent to megestrol acetate as second-line therapy for metastatic breast cancer; now most recently, such agents have been shown to be equivalent and perhaps superior to tamoxifen in the first-line treatment of metastatic disease. Randomized trials comparing anastro-zole to tamoxifen and to the combination in the adjuvant setting have been completed. Results of these trials are expected within the next few years.

Other adjuvant trials incorporating aromatase inhibitors are in progress. In some of these trials, aromatase inhibitors are being administered following tamoxifen; examples include the European for Research and Treatment of Cancer (EORTC) randomized trial of exemestane vs additional tamoxifen after 3 years of adjuvant tamoxifen therapy, and a randomized trial of letrozole vs placebo after 5
years of tamoxifen in the postmenopausal adjuvant setting [NCIC CTG trial MA.17]). In other trials, such as the ATAC trial, aromatase inhibitors are being used in combination with tamoxifen. Thus, the role of the aromatase inhibitors in the adjuvant treatment of postmenopausal women will be better defined over the next few years.

**Treatment Recommendations**
Currently, for postmenopausal women with estrogen or progesterone receptors that are positive, tamoxifen therapy for 5 years is recommended. For women at intermediate risk of recurrence, the addition of combination chemotherapy, either standard Bonadonna CMF or AC, could be recommended. In higher-risk women, combination chemotherapy with other anthracycline combinations, such as CEF (cyclophosphamide, Epirubicin, and 5-Flourouracil) or AC/Taxol, may be appropriate. It seems clear that the addition of combination chemotherapy to tamoxifen is beneficial, but whether it should be recommended in an individual case may depend on the underlying level of risk of recurrence.

**Use of Bisphosphonates**

Seven or eight large randomized studies have shown that bisphosphonates, administered either orally (eg, clodronate [Bonefos, Ostac]) or intravenously (eg, pamidronate [Aredia]), are extremely effective in the treatment of women with established bone metastases from breast cancer.[48] In randomized, placebo-controlled studies, these drugs have been shown to reduce the number of skeletal-related events, an outcome measure that includes fractures, surgical orthopedic procedures, and a requirement for radiation to painful bony areas. In most studies in which they were carefully measured, pain control and quality of life were also improved by the use of a bisphosphonate. A number of groups now have formal guidelines on the use of bisphosphonates.[49] It is unclear whether bisphosphonates are also useful in women who have metastatic disease that does not involve bone, but at least one study has suggested that this may be the case.[50] Furthermore, several studies evaluating either pamidronate or clodronate in the adjuvant setting have suggested that their use may prolong the interval to the development of bone metastases.[51,52] In one somewhat anomalous study, Diel et al[51] showed that the use of bisphosphonates in the adjuvant setting, in a group of women selected to be at particular risk for bone metastases because of bone marrow involvement at the time of initial diagnosis, produced not only a reduction in bone metastases but a reduction in metastases to other distant sites and an improvement in survival.[53] Numerous ongoing trials are exploring the use of bisphosphonates in the adjuvant setting. As a result, the role of these agents as adjuvant therapy should be clarified in the near future.

**Summary**

Endocrine treatment remains important for women with breast cancer in both the metastatic and adjuvant settings. The exact combination and sequence of hormonal agents are still under investigation, although more is known about these drugs with every passing year. The addition of the bisphosphonates in metastatic disease has also proved helpful in improving quality of life. Randomized trials have greatly clarified the exact roles of the more established endocrine agents in breast cancer treatment. However, in addition, a variety of new agents are currently under development. These include the pure antiestrogens, such as ICI 182,780 (Faslodex); selective estrogen receptor modulators (SERMs), such as raloxifene (Evista) and idoxifene; and a group of drugs that may have effects intermediate between the antiestrogens and SERMs, such as EM 652 (SCH57068, Schering).

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