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Endocrine therapy for advanced breast cancer: a review

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Summary

More than 45,000 women will die of metastatic breast cancer in the United States in 1991. Endocrine therapy remains a major option for treatment of such patients, and results in complete plus partial response rates of 30% with a median duration of approximately one year. Postmenopausal status, increased age, a prolonged disease-free interval, bone and soft tissue metastases, and positive estrogen and progesterone receptors are all associated with an increased response to endocrine therapy. The use of additive hormonal therapy, specifically antiestrogens, progestins, and aromatase inhibitors, have replaced surgical ablative procedures in the majority of patients; response rates to antiestrogen therapy, progestin therapy, and aromatase inhibitors are similar, but antiestrogens have generally been associated with the most favorable therapeutic index. At present, there is no convincing evidence that either combinations of endocrine therapies or endocrine therapy combined with chemotherapy are associated with an improvement in survival for patients with metastatic disease. Future research efforts directed at defining the molecular mechanisms of endocrine activity should facilitate clinical trials of newer and potentially more effective agents. All patients with metastatic breast cancer should be considered for at least one trial of endocrine therapy provided their metastatic disease is not rapidly progressive or life-threatening.

Introduction

The demonstration by Beatson in 1896 that oophorectomy could result in regression of skin metastases in a women with breast cancer provided the foundation for investigations of endocrine treatment [1]. Subsequent research focused on other methods of endocrine ablation for both initial and subsequent treatment. Although adrenalectomy and hypophysectomy proved to be effective palliative maneuvers, in some series morbidity and mortality were substantial. Subsequently, estrogens, androgens, and progestins became available and demonstrated response rates similar to ablative procedures [2-5]. More recently, antiestrogens [6,7] and aromatase inhibitors [8,9] have been shown to be as effective as other endocrine modalities. Several excellent reviews have described the role and use of endocrine therapy in metastatic breast cancer [2-5, 7,10,11]. This overview will help provide clinical guidelines for the selection of endocrine therapy.

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Selecting patients for endocrine therapy

Factors that help predict the likelihood of response to endocrine therapy are presented in Table 1. Estrogen receptor (ER) and progesterone receptor (PR) status are the most effective prognostic tools; patients who are both ER- and PR-positive display response rates of approximately 70% compared to response rates of ≤20% in patients who are ER- and PR-negative [3,12]. In a detailed review by Henderson [5], between 43 and 62% of ER-positive patients responded to a variety of endocrine therapies compared to 6 to 10% who were ER-negative. Several factors may account for the paradoxical effect of a response to hormone treatment in a patient with a receptor negative tumor. First, estrogen and progesterone receptor distribution is heterogeneous within the initial site of the tumor, as well as among different metastatic sites [13-15]. Second, improper handling of tumor specimens may result in depletion of receptors and false negative results. Third, non-endocrine mechanisms resulting in tumor cytotoxicity may occur [16,17]. Finally, even in patients whose tumors are ER- and PR-negative by cytosol analysis, immunohistochemical methods frequently demonstrate small numbers of receptor-positive cells. Such cells when stimulated by hormonal agents may secrete transforming growth factors (TGF's) such as TGF-ß which may suppress growth and division of surrounding receptor-negative tumor cells [16,17].

The site of metastases is also related to response, though endocrine therapy may cause tumor regression in any metastatic site, including the central nervous system. Patients with soft tissue or bone metastases are more likely to respond to endocrine therapy than patients with visceral disease [7,18], and such metastatic sites have also been shown to contain tumor cells more likely to be ER-positive [19]. In addition, studies have shown that patients with ER-positive primary lesions are more apt to develop bony metastases than patients whose tumors are receptor-negative [20]. These data suggest a biologic relationship between the site of metastases and the receptor status of the tumor. Such data are provocative, and further research directed at defining the molecular basis of such relationships would help interpret the biology of breast cancer metastases.

In addition to receptor status and metastatic site, menopausal status, patient age, the disease-free interval (DFI), and prior response to endocrine therapy are also important predictors of response. Responses to endocrine therapy, with the exception of ovarian ablation and LHRH agonists, are more frequently observed in postmenopausal patients [3,21]. Whether this relationship is due to the lower frequency of receptor positive tumors in premenopausal patients is

Table 1. Factors associated with an increased response to endocrine therapy

Variable	% Response
Estrogen and Progesterone Receptor[1]	
ER+ / PR+	70%
ER+ / PR–	30%
ER– / PR+	40%
ER– / PR–	<10%
Site of Metastases[2]	
Soft tissue	30-60%
Bone	20-50%
Lung-pleura	20-40%
Liver	5-30%
Menopausal Status[3]	
Premenopausal	30%
Postmenopausal (>5 years)	30-35%
Perimenopausal	20%
Age (years)[3]	
30-39	20%
40-49	30%
50-59	30%
60-69	37%
≥70	46%
Disease-Free Interval[4]	
<5 years	30-42%
>5 years	56%
Prior Response to Endocrine Therapy[5]	
Yes	35-60%
No	17-30%

Modified from: [1] Osborne [12]; [2] Petru [7]; [3] Beex [21]; [4] Henderson [5]; [5] Wilson [28]

uncertain [12]. Increasing time from diagnosis to disease recurrence (DFI) has been consistently demonstrated to be related to endocrine responsiveness [5]. Patients with a DFI longer than 5 years have a significantly greater chance of responding to endocrine therapy than patients with shorter intervals. The DFI provides a "window" for the clinician to estimate the pace of the metastatic growth; patients with a long DFI have superior survival from the time metastatic disease is first detected, most likely related to slower tumor cell proliferation. These observations are supported by flow cytometry [22-25] and thymidine labelling studies [26,27] in patients with early stage breast cancer; patients who have primary tumors with low S-phase activity or low thymidine labelling have longer times to relapse.

Patients with metastatic disease who respond to endocrine therapy and then progress are more likely to respond to subsequent endocrine treatment than those who initially progress [5]. In one review, approximately 30 to 60% of patients who responded to an initial endocrine treatment also responded to secondary therapy, as opposed to 15 to 30% of those who did not initially respond [28].

Although the use of the factors above may be helpful in selecting patients and predicting response to endocrine therapy, it is this author's opinion that all patients with metastatic breast cancer, except for those with rapidly progressive disease, should be considered for a trial of endocrine treatment. Since the treatment of metastatic breast cancer is palliative irrespective of whether one uses endocrine therapy, chemotherapy, or both, a trial of endocrine therapy, which is generally associated with only modest toxicity, should be considered even for patients unlikely to respond. In one randomized trial comparing endocrine therapy with chemotherapy in women greater than 65 years, it was found that survival was not influenced by initial choice of treatment [29]. Although the response to cyclophosphamide, methotrexate, and fluorouracil (CMF) was higher in the estrogen receptor negative patients than the response to tamoxifen (43% versus 21%), patients failing tamoxifen subsequently responded to chemotherapy without reduction in overall survival. In a similar randomized trial, the response to chemotherapy (45%, cyclophosphamide and doxorubicin), or chemotherapy and concurrent tamoxifen therapy (51%), was significantly higher than the response to tamoxifen alone (22%) in a group of patients with metastatic disease [30]. Nonetheless, patients treated with chemotherapy after progression on tamoxifen had an overall response rate of 43%, similar to patients who had initially received chemotherapy or combined therapy; survival of the three treatment groups was not significantly different. These data suggest that whereas patients with metastatic disease generally have a higher initial response to chemotherapy than to endocrine therapy, an initial trial of endocrine therapy does not compromise overall survival.

Ablative therapy

Both irradiation and surgical oophorectomy remain viable treatment options for premenopausal patients, with overall response rates of 30%; responses are uncommon in postmenopausal patients [31]. The use of either hypophysectomy or adrenalectomy cannot currently be recommended as a major treatment option. Hypophysectomy and adrenalectomy display similar response rates of approximately 30 to 40%, but their associated mortality rates of 1 to 5% [5] and high morbidity make them less desirable as options for initial and salvage therapy. Moreover, randomized trials comparing medical adrenalectomy with tamoxifen [32] and aromatase (estrogen synthetase) inhibitors such as aminoglutethimide [33] have demonstrated similar effectiveness. Hypophysectomy and tamoxifen [34] and aminoglutethimide [35] displayed similar results in two small randomized trials. Newer procedures for hypophysectomy such as the transsphenoidal approach or implantation with radioactive seeds have reduced morbidity and mortality but are still of much greater risk than additive therapies [5].

Additive therapies

Selected endocrine agents, their commonly used doses and schedules, and major toxicities are presented in Table 2. Tamoxifen probably represents the most widely used agent for metastatic breast cancer because of its modest toxicity profile and its effectiveness in both pre- and postmenopausal women. For patients who have tumor progression while taking tamoxifen or in the small percentage of women who must be removed from tamoxifen treatment because of intolerable side-effects, oophorectomy (in premenopausal women) or progestins represent the next major option. Although progestins are not superior in effectiveness to aromatase inhibitors, they are generally less toxic. LHRH agonists should be reserved for treatment of premenopausal women and estrogens and corticosteroids for treatment of postmenopausal women. Androgens are probably less effective than other agents but may induce response in both pre- and postmenopausal patients.

Antiestrogens

Tamoxifen is a synthetic antiestrogen that has been shown in randomized trials to be as effective as all other available endocrine therapies including estrogens, oophorectomy, progestins, and aminoglutethimide [3,5,36]. When tamoxifen is given as initial therapy, responses are noted in 30 to 40% of patients and generally last approximately 1 year; withdrawal (rebound) responses in patients who have responded and subsequently

Table 2. Endocrine therapies — agents, dose and schedule, and toxicity

Agent	Dose and schedule	T 1/2	Common toxicities[1]
Estrogens			
Stilbestrol(DES)	5 mg tid	24 hr	Nausea, vomiting, sodium retention, uterine bleeding, breast tenderness and engorgement, nipple pigmentation.
Ethinyl estradiol	0.5-1.0 mg tid	28 hr	
Antiestrogens			
Tamoxifen	10 mg bid	4-14h,>7d	Hot flushes, menstrual irregularities, vaginal discharge.
Progestins			
Medroxyprogesterone	400 mg daily	1h,4h	Weight gain, withdrawal bleeding, fluid retention.
Megestrol	40 mg qid	4h	
Aromatase Inhibitors			
Aminoglutethimide	250 mg bid-qid	7-13h	Nausea, vomiting, skin rash, lethargy.
Androgens			
Fluoxymesterone	10 mg bid-tid	9h	Masculinization, nausea, vomiting, cholestatic jaundice, fluid retention.
LHRH Agonists			
Leuprolide	Depot 7.5 mg	—	Hot flushes, amenorrhea, nausea, vomiting.
Goserelin	Depot 3.6 mg	—	
Corticosteroids			
Prednisone	15-40 mg daily	30 min	Mood disturbance, proximal muscular weakness, osteoporosis, bone loss, Cushingoid appearance, immunosuppression.

[1] Only common toxicities are listed. See package inserts for complete details.

Data from Swain and Lippman [11], Dorr and Fritz [84], Henderson [5], and Physicians Desk Reference (Medical Economics Co, Oradell NJ, 1991)

progress have been described in as many as 20% of patients [37]. The mechanism of the withdrawal response is unclear, but in one trial patients with tumor progression had subsequent decreases in dehydroepiandrosterone (DHEA), estrone, and estradiol after tamoxifen was discontinued; when tamoxifen was reinstituted in patients who had hypophysectomy or oophorectomy, levels of all three steroids dramatically increased [38]. The authors suggested that in some patients tamoxifen was able to stimulate adrenal production of DHEA which was subsequently aromatized to estrogen resulting in tumor stimulation. Tamoxifen has been associated with a tumor flare in approximately 5% of patients with skin or bone metastases. Flare generally occurs within days or weeks of beginning treatment [39,40], and may be manifested by an increase in size, number, and discomfort associated with skin lesions, and by increasing bone pain and hypercalcemia in patients with bone metastases. Patients should be informed of such reactions and instructed to report symptoms of increasing bone pain or hypercalcemia to their physician. Although controversial, patients who develop tumor flare frequently respond to therapy; patients may continue tamoxifen and be treated symptomatically until symptoms improve, or tamoxifen may be stopped and restarted. Flare may also be seen with estrogens or androgens, and less commonly with progestins or ablative therapy [39]. Patients who display progression of skin lesions or increasing bone pain after several months of tamoxifen generally have tumor progression and not tumor flare. Although several reports have suggested that patients failing standard tamoxifen dosage may respond to a higher dosage given subsequently, such responses are infrequent [36], and other agents should be considered.

New antiestrogens including toremifene [41], droloxifene (3-hydroxy-tamoxifen) [42], and trioxifene [43] are currently under investigation. Further trials will be needed to determine whether these agents will prove either to be superior to tamoxifen in inducing or prolonging response, or to be similar in efficacy but with less toxicity.

Progestins

Progestin therapy has become increasingly popular for the treatment of metastatic breast cancer [5,7,44-46]. Medroxyprogesterone acetate (MPA), megestrol acetate (MA), and other progestins result in response rates of 20 to 40% in patients with metastases, and in randomized trials have been equal in efficacy to tamoxifen and other endocrine agents. Progestins display minimal toxicity when used in standard dosage, however many patients will experience major weight gain after prolonged treatment. Several Phase II trials have suggested that high dose MPA may be superior to the standard dosage [47], although randomized trials comparing high and low dosage of this agent have been inconclusive [48-52]. In the United States, most trials of progestin therapy have utilized the oral progestin megestrol acetate (Megace^{T}) [53]. Megestrol acetate is well tolerated and generates serum levels of progestin similar to high dose MPA. In one trial, the use of high dose megestrol after failure of the standard dose (160 mg daily) was associated with response or stabilization of disease in 13 of 17 patients [54], but in another trial no response was observed in 34 patients given 800 mg daily after progression on 160 mg daily [55]. Recently, a randomized trial comparing standard with high dose megestrol acetate has shown a significant improvement in response rate, time to progression, and survival favoring the high dose agent [55]. Other trials currently in progress comparing high and low dose megestrol acetate (Cancer and Acute Leukemia Group B Protocol 8741) will hopefully confirm the results of this study. Recently, antiprogestins have been developed, and mifepristone (RU486) has shown activity in early clinical trials [56]. Further investigations of antiprogestins should be forthcoming.

Aromatase inhibitors

In postmenopausal women, conversion of the adrenal steroid androstenedione to estrone (and

subsequently to estradiol) at peripheral sites is the major mechanism of estrogen production. Aromatase (estrogen synthetase) is the main enzyme involved in this process, with its greatest concentration in adipose and hepatic tissues [8,57,58]. At low concentration, aminoglutethimide exerts its greatest inhibitory effect on aromatase. Aminoglutethimide in higher concentration inhibits adrenal steroid synthesis directly, further depleting adrenal androgen production and ultimately estrogen. Numerous studies have demonstrated the effectiveness of aminoglutethimide for endocrine treatment of metastatic breast cancer [3,8,57,58]. Several randomized trials have confirmed that this compound is as effective as progestins or tamoxifen as both initial or secondary therapy [5,8]. Postmenopausal patients derive the major benefit from aminoglutethimide treatment, but responses have been observed in one small series of premenopausal patients [59]. Severe myelosuppression has been reported in less than 1% of patients [60], but lethargy (36%), a maculopapular rash that occurs during the first two weeks of therapy and which usually resolves despite continued treatment (25%), dizziness (15%), and nausea and vomiting (10%) have made it a less desirable treatment option than tamoxifen or progestins [58]. The standard dosage of 250 mg four times daily requires concomitant use of hydrocortisone (40 mg daily) to prevent hypoadrenalism, but randomized trials have shown that lower doses of 250 mg twice daily are as effective and can be given without steroid supplementation [5]. Hydrocortisone supplementation is not necessary for patients treated at lower dosage, but should probably be given in hopes of minimizing toxicity; corticosteroids may also enhance the response to aminoglutethimide though this is unlikely.

Newer aromatase inhibitors such as 4-hydroxyandrostenedione appear equal in efficacy to aminoglutethimide in early clinical trials, and have less toxicity [61,62]. Trilostane, an inhibitor of adrenal steroid synthesis, has also been shown to be effective in postmenopausal patients, but has substantial toxicity and requires concurrent corticosteroid administration [63-65]; it is doubtful that this compound will prove to be of major value. Ketoconazole also interferes with steroidogenesis and might prove an active agent, but its substantial toxicity makes it unlikely to find a role in clinical practice [3,66].

Estrogens

Although not widely used, estrogens remain effective agents for postmenopausal patients, displaying response rates of 20 to 40%. Among the compounds available, diethylstilbestrol (DES), ethinyl estradiol, and conjugated estrogens remain the most commonly used preparations; no large randomized trials of the different estrogen preparations are available but it is unlikely that major differences in outcome would be related to the type of estrogen used. Controversy still exists as to whether estrogens display a dose response effect, but in one large trial of DES, major differences in dosage had no consistent effect on outcome [67]. Up to 30% of patients given estrogen therapy display nausea and vomiting, and anorexia, uterine bleeding, breast engorgement and pain, urinary symptoms, and edema are also common. Thrombophlebitis and congestive heart failure occur in a small percent of patients. Estrogen therapy is still worthy of consideration in patients who have been previously responsive to endocrine therapy. Patients may be started on 5 mg daily of DES with escalation to 15 mg daily over several weeks to attempt to diminish nausea, vomiting and other undesirable side-effects associated with the initiation of treatment. Patients unable to tolerate higher doses may be maintained at a lower dose in an effort to achieve response.

Corticosteroids

Corticosteroid therapy has been associated with response rates of 20 to 25% [3], rates generally lower than for most other agents. In women older than 65 years who had failed primary endocrine treatment, prednisolone 15 mg daily caused tumor regression in 14% and stabilization

for greater than or equal to six months in 21% [68]. In seriously ill cancer patients, a comparison of corticosteroid therapy with placebo has shown a significant improvement in sense of well being, appetite, and functional status for patients taking steroids [69]. Because of the major undesirable side-effects associated with chronic use, corticosteroids should be reserved for use until after other more effective and less toxic agents have been tried.

Androgens

Response rates to androgens including testosterone, fluoxymesterone, testolactone, and calusterone have been noted in approximately 20% of patients [5]. Masculinization, including deepening of the voice and hirsutism, occurs in 60 to 70% of patients, and hair loss, acne, and increased libido in 20 to 40% [3]. Tumor flare and hypercalcemia may also be more common with androgens than other hormonal agents [39]. The low response rate and high toxicity profile make androgens a less desirable choice than other endocrine agents.

Danazol, a weak androgen that inhibits gonadotropin secretion, has displayed response rates of 5 to 15% in patients who had received prior endocrine therapy; moderate side-effects were noted in approximately 25% [70-73]. Danazol might be considered for salvage therapy in patients who have become refractory to other agents.

Anti-androgens such as flutamide and cyproterone acetate have received only limited evaluation, although in one trial only a single partial response was found in 29 evaluable patients given flutamide 750 mg daily [74]. In this latter trial the majority had received prior endocrine therapy, and 17 patients were receptor-negative.

Luteinizing hormone releasing hormone (LHRH) agonists

LHRH agonists, including leuprolide (Leupron), buserelin, and goserelin (Zolodex), although not approved for use in carcinoma of the breast, have been associated with response rates approximating 35 to 40% in premenopausal women [5]. Response in postmenopausal patients has generally been less than 10% [5]. LHRH agonists suppress release of FSH and LH, causing a "medical oophorectomy" and lower estrogen levels. Currently, depot forms of LHRH agonists have made this therapy extremely convenient, and a monthly schedule of treatment can be used. Side effects with these agents are minimal and include cessation of menses, hot flushes, and occasional nausea (75). These agents should be considered for premenopausal patients responsive to prior endocrine therapy.

Prolactin antagonists

Prolactin has been shown to be a potent growth regulator in many animal tumor models, but plays a questionable role in human breast cancer [33]. Levodopa (L-DOPA), which suppresses prolactin levels, may relieve metastatic bone pain but has no clearly defined current role in the management of metastases [76]. Bromocriptine, either alone (77) or in combination with a somatostatin analog (78) appears to have only minimal activity.

Combination endocrine therapy

Combination therapy utilizing more than one endocrine agent given simultaneously has been extensively studied [3,5]. Although in some phase II and phase III trials, several combinations displayed higher initial response rates than single agent therapy, randomized trials have not shown that any combination of agents convincingly improves survival when compared to single agent treatment. In addition, the overall or additive response rates appear similar for combination and sequential therapies [3]. Moreover, toxicity profiles and costs of combination therapy are frequently much greater than for single agent

treatment. Recently, the combination of tamoxifen and fluoxymesterone was found to be associated with a significantly higher response rate (61% versus 42%) and median time to progression (12.9 months versus 7.4 months) than tamoxifen alone in 97 patients over age 65 years with an ER value of 10 or greater [79]. This trial, though provocative, requires further confirmation before such treatment should be accepted as superior to less costly and less toxic single agent treatment.

Multimodality treatment with endocrine therapy and chemotherapy

Numerous phase II and phase III trials have studied combined modality therapy using both hormonal and cytotoxic agents. Although in several of these trials a significantly higher initial response rate was noted for the combination, overall survival has rarely been significantly prolonged [3]. In one randomized trial, the addition of cyclophosphamide and fluorouracil to DES in 40 patients with receptor-rich metastatic breast cancer significantly increased median survival from 29 to 72 months when compared to DES alone; no benefit of combined therapy was seen in patients who were receptor-negative or unknown [80]. Because most randomized trials have failed to demonstrate a compelling survival advantage, it is this author's opinion that chemotherapy should be reserved for patients who fail endocrine therapy, and should not be given concurrently. Since chemotherapy is generally more toxic as well as more costly, initial endocrine treatment should result in a higher quality of life. In addition, responses to therapy can be more accurately assessed when chemotherapy and endocrine therapy are given sequentially; responses to combined therapy might be due to the endocrine modality, the chemotherapy modality, or both. Moreover, in vitro data has suggested that certain endocrine agents such as antiestrogens as well as progestins may decrease tumor cell proliferation and antagonize the effects of chemotherapy [81,82]. Though such antagonism has not been demonstrated (or vigorously evaluated) in clinical trials, these data provide further rationale for sequential therapy. It is this investigator's opinion that only in patients with rapidly progressive visceral disease should combined modality therapy be considered. In this setting, utilization of an antiestrogen with an anthracycline or other agent that has not been shown to antagonize the effectiveness of chemotherapy in vitro should be considered.

Conclusions

Endocrine therapy gives the clinician the option of providing effective treatment for metastatic breast cancer with limited toxicity. Although agent selection may be a formidable task, a suggested approach to endocrine therapy selection is presented in Table 3. For patients who develop metastases while receiving tamoxifen as adjuvant therapy, observing the patient for a withdrawal response or beginning second line endocrine therapy will depend on the site of relapse and the clinical status of the patient. In patients who have received adjuvant tamoxifen and relapse after completing tamoxifen therapy, rechallenge with tamoxifen may result in a durable remission [83]. In patients with slowly progressive disease, who have minimal symptoms, the use of multiple successive single agent treatments is appropriate even if none convincingly induce tumor response. Although the likelihood of response is reduced for each successive hormonal manipulation, all current therapy in the metastatic setting is palliative, and quality of life is probably benefitted by continued treatment with less toxic endocrine agents. In patients with worsening symptoms, or rapidly progressive disease as judged by clinical or laboratory findings, chemotherapy should be instituted. The greater toxicity of chemotherapy in these patients is warranted as further endocrine manipulation is unlikely to be of benefit. Defining the molecular mechanisms responsible for endocrine responsiveness is a major focus of research activity, and such information will undoubtedly result in the

Table 3. Guidelines for treatment selection

Premenopausal patients:

1. Start with tamoxifen.
2. If patient responds, then at progression consider observing for withdrawal response if patient has minimal symptoms and no major organ dysfunction. If major symptoms or organ dysfunction, consider oophorectomy.
3. When the patient progresses, consider further endocrine therapy with progestins, aminoglutethimide, or LHRH agonists for responders, or for nonresponders with indolent disease.
4. Androgens or corticosteroids should be considered for patients who have responded to the above or those with indolent disease and a paucity of symptoms.

Postmenopausal patients:

1. Same strategy as above except:
   a. Oophorectomy and LHRH agonists are unlikely to be of value and should not be major considerations for treatment.
   b. Progestins followed by aminoglutethimide should be considered for responders or for those with indolent disease.
   c. Estrogens and corticosteroids should be considered before androgens.

For all patients:

1. Watch for tumor flare and hypercalcemia. Manage symptomatically and hold therapy for severe symptoms or hypercalcemia with neurologic or electrocardiographic abnormalities.
2. Bone lesions frequently respond slowly and patients may show worsening of laboratory values (alkaline phosphatase), tumor markers (including CEA and CA-15-3) or conventional x-rays (increase in size and number of blastic lesions) over the first several months of treatment. Patients with improvement of pain and who are doing well clinically should be kept on treatment unless there is convincing evidence of disease progression.

development of more effective endocrine therapies. Currently, single agent therapy remains the standard endocrine approach for women with metastatic breast cancer.

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