The Treatment of Metastatic Breast Cancer

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Introduction

Fifty percent of all women who have had breast cancer will eventually develop metastases, a stage at which the disease is seldom curable. Metastatic breast cancer may affect any tissue in the body.[1] The duration of the "free interval," the interval between the initial diagnosis of breast cancer and the detection of the first metastasis, is extremely variable. Adjuvant chemotherapy is frequently given as part of the primary treatment of breast cancer. As early as 1958, some of the first National Surgical Adjuvant Breast and Bowel Project (NSABP) trials demonstrated that adjuvant chemotherapy could increase both disease-free and overall survival.[2–4] Scandinavian studies with more than 15 years of follow-up confirmed these findings.[5] In spite of this, the total mortality from metastatic disease remains unchanged. Treatment of advanced breast cancer is therefore of major importance in the management of this disease.

The aspects to be considered in treating metastatic breast cancer are the timing and selection of therapy, based on both the disease and the individual patient, and the management of complications, both of the cancer and the treatment.

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Treatment Considerations

Timing

In selecting the best time to start treatment, the clinician should evaluate the site of metastatic involvement, the patient's symptoms, the apparent growth rate of the tumor, the extent of disease, and the patient's hormone-receptor status. For example, totally asymptomatic osteoblastic metastases found incidentally during the clinical evaluation of a postmenopausal woman with hormone-receptor-positive breast cancer may remain stable for months and sometimes years without any treatment.

Characteristics of the Cancer

Locoregional recurrences, solitary metastases, and metastases involving particular organs or locations may require specific local treatment in addition to systemic therapy.[6] Such local therapy may include surgery, radiotherapy, regional chemotherapy, and embolization, alone or in combination.

Certain biological characteristics, such as the hormone-receptor status, free interval, extent of tumor dissemination, major tissues affected, and estimated rate of growth, may also help in the selection of the treatment.

Patient Characteristics

Certain preexisting medical problems may contraindicate specific treatment options or

indicate the need for very close monitoring. These include hypertension, diabetes mellitus, peptic ulcer, and certain psychiatric states that may be exacerbated by steroid agents. Cardiac and pulmonary conditions may increase the hazards associated with anthracyclines, cyclophosphamide, and methotrexate. Similarly, impaired renal or hepatic function may limit the dosage or even the use of certain cytotoxic agents. Advanced age and a frail general condition may impose limitations on the use or optimal intensity of cytotoxic regimens, thus limiting treatment to palliation.

Complications of the Disease

Complications related to the disease can include mechanical problems, such as pathologic fractures of long bones; effusions in serous cavities (such as the pleura, pericardium, and peritoneum); and compression or obstruction of important vascular, neurologic, gastrointestinal, urinary, or respiratory structures. Possible complications of the cancer also include metabolic problems, of which hypercalcemia is the most common in breast cancer.

Complications of Treatment

Bone marrow suppression with leukopenia and thrombocytopenia is the most common complication of chemotherapy and seldom requires specific management other than in the context of trials of intensive chemotherapy with autologous bone marrow transplantation rescue. The most common metabolic problems are those related to the exacerbation of diabetes and to electrolyte disturbances caused by corticosteroids. Cardiovascular complications include increased hypertension due to steroid hormones and toxic cardiomyopathy due to anthracyclines. While hypertension is manageable, cardiomyopathy can be progressive and severely disabling. In dealing with treatment-related complications in general, anticipation, early detection, and, if possible, prevention constitute the best approach.

Treatment selection requires the following preliminary information:

- A complete chronologic history of the cancer, including evaluation of the free interval; information about the hormone-receptor status of the primary tumor and, whenever available, of any recently biopsied metastatic tumor; and information about the menstrual status of the patient.
- A detailed previous history and complete systems review.
- A careful evaluation of the patient's symptoms, including their location, duration, and progression.
- An evaluation of the extent of metastases based on physical examination; blood tests (including tumor markers such as carcinoembryonic antigen [CEA] and CA15-3); chest x-ray; bone scan; and spot x-ray of areas seen as abnormal on the scan, liver scan, or computed tomography (CT). The value of routine initial brain CT, however, is still open to question.

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- Careful questioning of the patient and review of records to obtain information about previous treatment, including response and specific details about any radiotherapy, such as the dose and the areas treated.

This basic information not only helps determine the choice of systemic therapy and prognosis but also establishes a baseline for evaluation of the response to the next treatment. For example, a slow progression of symptoms in a postmenopausal woman with a hormone-receptor-positive cancer, which is mainly skeletal in distribution, indicates a high likelihood of response to hormonal treatment. In a premenopausal woman, a slow progression of symptoms may be a good indication for bilateral oophorectomy.

The use of bone x-ray films in addition to bone scan will help to evaluate the status

of these metastatic lesions. While they may appear similar on bone scan, they may be either osteoblastic, osteolytic, or mixed on x-ray films. A change in appearance from osteolytic to osteoblastic under treatment usually signifies healing, although the lesions may look more intense on the bone scan.[7] Such an increase in intensity may also occur if the lesion progresses and becomes osteolytic on x-ray. Therefore, while bone scan is extremely sensitive for the detection of bony metastases, x-ray should be used as a complementary evaluation technique.

The blood tests performed reflect abnormalities of function of different tissue systems—the blood count reflecting the bone marrow; and the serum chemistries reflecting liver function, bone tissue activity, renal function, and other metabolic changes. These changes, however, are not specific for cancer and may only indicate the possibility that a problem exists in one or more given organs. Abnormal levels of CEA and CA15-3 usually indicate the presence of active breast cancer. While the sensitivity of these tests is limited, their specificity makes them useful in the evaluation and follow-up of the course of the disease.

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With the increasing effectiveness of systemic therapy, more patients are surviving long enough to manifest late incidence of cerebral metastases. Some of these metastases remain silent for undetermined periods of time before signs and symptoms become apparent, usually confirmed by a brain CT. It is not known, therefore, whether earlier detection and treatment of such lesions would favorably influence survival and quality of life.

In summary, there is no single parameter that will by itself determine regression, arrest, or progression of metastatic disease. The early detection of the metastatic spread of breast cancer must therefore be based on a multimodal diagnostic plan.

While it stands to reason that the smaller the tumor burden (that is, the earlier the detection of metastatic disease), the more effective the treatment, proof of this thesis is lacking.[8]

There is still no valid evidence that treatment of asymptomatic metastatic breast cancer results in any advantage in quality of life or overall survival. It is unclear whether this is because the usual present method of search for metastases results in the detection of only the more advanced stages of this disease. The questions remain: Could more frequent, more intense, or more specific and sensitive diagnostic tests result in much earlier diagnosis, and could earlier treatment change the spectrum of this disease?

Once metastatic disease is discovered and it is determined that treatment is indicated, a decision must be made about the most appropriate therapy.

Endocrine Therapy

The growth and clinical course of breast cancer is frequently influenced by the hormonal milieu of the patient. This fact was known long before the discovery of hormone receptors. Indeed, until the early 1960s, endocrine treatment was the major effective therapy for metastatic breast cancer and its potential effectiveness was based entirely on clinical criteria: patients whose metastatic disease was limited in extent, was mostly osseous, and occurred after a long free interval were known to have a high likelihood of response.

The development of methods that could determine the presence and concentration of estrogen receptor (ER) and progesterone receptor (PR) in breast cancer tissue[9] improved the selection of patients who could best benefit from endocrine therapy. It was observed that patients with breast cancer known to have a relatively high concentration of ER and/or PR (i.e., who were hormone-receptor-positive) had a better prognosis.[10,11] These women generally responded well to endocrine therapy,[12]

while the converse was also true—i.e., patients whose breast cancers were hormone-receptor-negative generally did not have much of a response to endocrine therapy. The higher the hormone-receptor concentration, the greater the response.[13,14]

Tamoxifen

Tamoxifen is the initial treatment of choice in postmenopausal patients with metastatic breast cancer that is either hormone-receptor-positive or has a clinical course indicative of potential hormone responsiveness. Tamoxifen therapy induces remission in 40 to 80 percent of such patients.[13] Some reports indicate results in premenopausal women similar to those obtained with oophorectomy.[15,16]

The optimal dose in postmenopausal women is 10 mg orally twice a day. In premenopausal women, the optimal dose might be higher, since higher levels of estrogens may displace tamoxifen from the receptor sites in tumor tissue.

The side effects of tamoxifen include initiation or worsening of the menopausal syndrome—hot flashes, atrophic vaginitis, dryness of mucous membranes (including dryness of the mouth and conjuctivae), and sometimes depression. Occasionally, vaginal bleeding may occur. Tamoxifen has, however, been reported to have a protective effect against osteoporosis.[17] Anorexia and nausea are rare and, when they do occur, mild and transient. Rarely, prolonged administration of tamoxifen has been reported to produce retinal changes with visual impairment. There may be also an increased risk of venous thrombosis.[18]

Transient exacerbation of symptoms of metastases may occur during the first two to three weeks of treatment but should not cause it to be interrupted. Hypercalcemia is a rare complication of treatment with tamoxifen. An increased incidence of endometrial cancer has been reported in women maintained on prolonged treatment with this medication.[19,20] These reports, however, have not been confirmed by any of the NSABP trials and should not limit the duration of use of tamoxifen in patients with metastatic breast cancer, where the actuality of the disease completely overshadows the potential risk of the treatment. Careful regular gynecologic examinations should be maintained, and periodic endometrial biopsies may be recommended in addition to the usual cytologic examinations of the vaginal and cervical smears.

Bilateral Oophorectomy

Bilateral oophorectomy is mainly used for the initial treatment of hormone-receptor-positive metastatic breast cancer in premenopausal women. The surgery carries a low morbidity and mortality. Its effect is rapid. The procedure never exacerbates the metastatic disease, and its major side effects are due to the induction of premature menopause, which must be considered an expected effect of the surgery rather than a toxic side effect. Bilateral oophorectomy induces a remission of metastatic disease in about 50 to 60 percent of appropriately selected patients with ER-positive breast cancer.[21] The combination of oophorectomy and cortisone has been reported to improve response,[22] presumably through suppression of adrenocortical estrogen precursors.

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Progestins

Two progestins have been used extensively in recent years: medroxyprogesterone acetate (standard dose of 400 mg intramuscularly daily) and megesterol acetate (standard dose of 160 mg orally daily). In randomized trials, these agents appear to be equally effective[23] when used as initial treatment. Larger doses may sometimes produce a response when standard doses remain ineffective.[24–26]

Progestins almost always cause weight gain[27] and sometimes sodium and fluid retention. These agents may also cause vagi-

nal bleeding while taken and, more frequently, after cessation of treatment.

Estrogens

Since the advent of tamoxifen, estrogens are seldom used in the treatment of metastatic breast cancer. The most common estrogen used was diethylstilbestrol. Estrogen therapy of breast cancer is associated with a high incidence of serious side effects—fluid retention, mastalgia, thromboembolic manifestations, vaginal bleeding, and occasional stimulation of the growth of the metastases, sometimes with hypercalcemia. In a patient who has failed to respond to initial and secondary endocrine therapy for metastatic breast cancer, the markedly reduced response rate to tertiary endocrine treatment no longer warrants the relatively high incidence of potentially serious side effects associated with estrogens. This is particularly true of elderly postmenopausal women with late-stage disease for whom estrogens had traditionally been the treatment of choice.

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Androgens

Although less effective than other forms of endocrine therapy, androgens are still used for the treatment of women with hormone-sensitive breast cancer. The use of androgens, however, has also decreased markedly since the development of tamoxifen. The most commonly used androgen is fluoxymesterone, which is administered mostly as a tertiary form of treatment in combination with cytotoxic agents in women with osseous metastases. It is also useful in myelophthisic anemia. The major side effects are related to masculinization—loss of scalp hair, hirsutism of the body and face, deepening of the voice, clitoral hypertrophy, and increased libido. Fluid retention and hypercholesterolemia are frequent. When fluoxymesterone is effective in causing regression of metastases, it also increases the feeling of well-being associated with a slight rise in the red blood cell count and an increase in muscle mass. This agent is effective in about 20 percent of patients but is also associated with a risk of occasional stimulation of the growth of metastases and of hypercalcemia.

Aminoglutethimide

Aminoglutethimide inhibits steroidogenesis in the adrenal cortex as well as aromatization of androgens to estrogens in peripheral tissues.[28] Because the optimal dose of 250 mg four times daily causes adrenocortical insufficiency, patients must therefore receive replacement doses of hydrocortisone of either 20 to 40 mg per day or the maximum that would not cause the development of Cushing's syndrome. Lesser doses of aminoglutethimide (250 mg twice a day) without hydrocortisone have been reported to be as effective as the larger doses in inducing remission of metastatic breast cancer.[29] This may indicate that the agent's major mode of action is through aromatase inhibition in peripheral tissues.

While aminoglutethimide is used mostly as second-line hormonal treatment in postmenopausal women, it has been reported to be as effective as tamoxifen as primary therapy.[30] Because of its toxic side effects, however, aminoglutethimide cannot be considered a primary treatment in the sequence of endocrine therapies. These side effects include somnolence, sometimes severe, and a drug rash that occurs in about 30 percent of patients and may be transient but is sometimes persistent, progressive, and increasingly severe enough to necessitate cessation of treatment. Nausea and hepatic dysfunction can also sometimes limit the use of this agent. The effectiveness of aminoglutethimide is markedly decreased in postmenopausal women when it follows a previous treatment that included prolonged administration of prednisone with resultant marked suppression of adrenocortical function and very low circulating levels of estrogen.[31]

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