Endocrine Treatment of Breast Cancer

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Endocrine therapy provides effective palliation for about 40 percent of women with recurrent or metastatic breast cancer. Extensive studies over the past 30 years have shown that various endocrine alterations can induce objective regression of breast carcinomas lasting a few months or several years. The mechanisms by which various endocrine therapies induce regression of human breast cancer are not fully understood. A working hypothesis maintains that the growth of some malignant tumor cells depends on hormonal function in the host, which is not unusual in kind or exaggerated in rate. Therefore, deprivation of essential hormones or interference with their action would cause growth cessation and eventual elimination of some of the cells, in the same manner that an endocrine target organ atrophies after removal of its essential hormone. This article deals with the use of systemic endocrine treatment and cytotoxic chemotherapy for the management of patients with recurrent or metastatic breast cancer. The author prefers sequential use of these two modalities.

Ovariectomy

Bilateral salpingo-ovariectomy is the initial treatment of choice for premenopausal patients with metastatic breast carcinoma. Patients are selected for this therapy on the basis of estrogen receptor measurements. (See Box) About 40 percent of unselected patients obtain objective remission of disease, which may last from three months to several years, with a median remission period of about one year. Patients who achieve remission after ovariectomy should be followed regularly, and at the first sign of reactivation of tumor growth, submitted to further endocrine therapy, preferably hypophysectomy. Patients who do not benefit from such as removal of the ovaries, the adrenal glands or the pituitary gland, yield optimum results. Often, patients may respond to more than one endocrine modality. Among adrenalectomy and hypophysectomy patients studied, (Table) were many who had previously undergone treatment by ovariectomy or the administration of pharmacological doses of the gonadal steroids.

Figures 1, 2 and 3 illustrate the extent of tumor regression that can be obtained with successful endocrine treatment. The table summarizes the results of various modalities of endocrine therapy. It is apparent that ablative procedures, supported by grants from the American Cancer Society, BC 61 P and the National Institutes of Health, CA-05197-16, RR0080-14 and CB 23859.

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Hormone Receptors

Elwood Jensen and his colleagues at the University of Chicago demonstrated that a specific estrogen binding protein is present in the cytosol of estrogen target tissues such as the uterus. They also showed that estrogen receptors can be detected in about 60 percent of primary breast cancers and in metastases. In addition, they correlated the presence of estrogen receptors in metastases with clinical response to endocrine therapy. We have confirmed these observations and use hormone receptors, when available, for selecting patients for endocrine therapy. Thus, when metastases contain measurable estrogen receptors, a remission rate of 60-70 percent has been obtained with adrenalectomy or hypophysectomy; when tumors have no detectable estrogen receptors, a remission rate of less than five percent has been achieved following ablative treatment. Preliminary results suggest that the presence of estrogen receptors in primary breast lesions can also predict response to subsequent endocrine therapy for metastatic disease appearing after a free interval. These findings indicate that the presence of estrogen receptors in breast cancer tissue is a useful marker for hormonal response. In those patients with tumors that lack estrogen receptors, systemic cytotoxic chemotherapy is initiated.

William McGuire and his colleagues at the University of Texas, San Antonio, demonstrated that progesterone receptors are present in about 60 percent of breast cancer specimens that contain estrogen receptors, whereas progesterone receptors are usually absent in those tumors that lack estrogen receptors. Clinical correlations are underway to determine whether progesterone receptors may provide a more reliable marker than estrogen receptors of clinical response to endocrine therapy.

Prolactin receptors have been found in low titers in 20-30 percent of human breast cancers. Clinical correlations between the presence of prolactin receptors and the response to endocrine therapy are not yet available. Studies of other receptors, such as androgens, corticoids, growth hormone and insulin, in breast cancer tissue are being carried out, but clinical correlations have not as yet been reported.

Hypophysectomy

Transnasal, transsphenoidal, microsurgical hypophysectomy is the initial treatment of choice for postmenopausal patients with metastatic breast carcinoma. In experienced hands, this procedure is well-tolerated and associated with minimal mortality, morbidity and side-effects. In a consecutive series of patients selected only on the basis of medical suitability for surgery, and eliminating those premenopausal women who failed to benefit from ovariectomy, we obtained an objective remission rate of 46 percent. This series includes many patients who underwent previous additive endocrine treatment, ovariectomy or cytotoxic chemotherapy. In a smaller consecutive series of patients with tumors that had measurable estrogen receptors, the remission rate was 73 percent. In patients who have had ovariectomy-induced remissions, about 90 percent experienced further objective improvement after hypophysectomy. The remissions lasted for a minimum of six months to several years, averaging about 18 months. Patients who obtain remissions are followed regularly. Combined cytotoxic chemotherapy is recommended at the first sign of reactivation of tumor growth. If the hypophysectomy has been complete, additive hormone therapy is usually ineffective after a hypophysectomy-induced remission; if the hypophysectomy has been incomplete, as determined by direct assay of ovariectomy, or those who do not have detectable estrogen receptors in their tumors, are treated with combined cytotoxic chemotherapy, since it is very unlikely that they will respond to other modalities of endocrine therapy. Castration can be effectively accomplished by radiation therapy to the ovaries, but there is a lag period of about six weeks before effective suppression of ovarian function occurs. Thus, surgical ovariectomy is usually preferred.
Fig 1. Regression following ovariectomy (a) Before treatment (b) After treatment
pituitary hormones, additive hormonal therapy may induce further periods of remission. Patients who fail to benefit from hypophysectomy invariably fail to benefit from further additive endocrine therapy and should be given cytotoxic chemotherapy.

Adrenalectomy
Bilateral salpingo-ovariectomy and adrenalectomy (or bilateral adrenalectomy in previously castrated patients) is recommended for postmenopausal patients with metastatic breast cancer, in the absence of an experienced neurosurgeon to perform a hypophysectomy. In experienced hands, this procedure is well-tolerated and is associated with minimal mortality, morbidity and side-effects in appropriately selected patients. In a previous, relatively unselected series of patients, we achieved a remission rate of about 40 percent. Other investigators have found a higher remission rate of 60 to 70 percent in patients with tumors that contained estrogen receptors, whereas in those with negative estrogen receptors, the remission rate was less than five percent. In a consecutive series of women who had ovariectomy-induced remissions, subsequent adrenalectomy produced a 50 percent remission rate. Only one randomized study, performed in England, has compared the results of hypophysectomy versus adrenalectomy; it showed that hypophysectomy increased the incidence and duration of remissions, as well as survival time. In our consecutive series of patients, remissions lasted from six months to several years, with a median duration of 12 months. This series also included many women who had undergone previous additive endocrine treatment and/or ovariectomy. Some patients who have a remission from adrenalectomy may further improve after additive hormone therapy; this is worth considering before cytotoxic chemotherapy is instituted. Although hypophysectomy has induced a few instances of regressions after adrenalectomy, performing both ablative procedures in the same patient is generally not indicated. Patients who do not benefit from ovariectomy and adrenalectomy almost invariably fail to respond to additive endocrine therapy, and combined cytotoxic chemotherapy is recommended.

Estrogens
Pharmacological doses of estrogens (Diethylstilbestrol, 5 mg. PO, t.i.d. or ethinyl estradiol, 1 mg. PO, t.i.d.) are most commonly used in women who are five or more years postmenopausal. In these patients, the objective remission rate is about 35 percent, with remissions lasting from three months to several years, and averaging about 12 months. When there is evidence of reactivation of disease, estrogen therapy should be withdrawn. Estrogen withdrawal may be associated with remission in some women, although the period of remission is usually of short duration. Patients who respond to estrogen therapy usually also respond to other modalities of endocrine therapy when the disease reactivates, especially hypophysectomy or adrenalectomy. Patients who do not benefit from estrogen therapy may nevertheless respond to other forms of endocrine therapy. For example, 60 percent of women over the age of 60 years obtain remission from hypophysectomy or adrenalectomy. Patients should be carefully observed during the initiation of estrogen therapy since exacerbation of disease may occasionally occur. In such an event, the hormone is abruptly withdrawn and other treatment instituted. The most common side-effect of estrogen therapy is fluid retention, which can be prevented by dietary sodium restriction and by the use of diuretics, when indicated.

Progestins
Pharmacological doses of progestins
Fig. 2. Regression following hypophysectomy (a) Before treatment. (b) After treatment.
Medroxyprogesterone acetate, 200 mg. PO, daily) induce objective remissions in about 30 percent of postmenopausal women with metastatic breast cancer for an average duration of about eight months. Patients who fail to respond, as well as those who have transient remissions from progestins, may obtain further remissions from other modalities of endocrine therapy. Progestin therapy is associated with minimal side-effects.

**Androgens**

Pharmacological doses of androgens (Fluoxymesterone, 10 mg. PO, b.i.d.) produce objective remissions, lasting about six months, in about 20 percent of postmenopausal women with metastatic breast carcinoma. Patients who do not respond to androgen therapy, as well as those who obtain transient remissions, may respond to other modalities of endocrine treatment. Fluid retention is a common side-effect and should be prevented by dietary restriction of sodium or by the use of diuretics, as indicated. Another side-effect of androgen therapy is virilization.

**Corticosteroids**

Pharmacological doses of corticosteroids (Prednisone, 30 mg. PO, q8h or Dexamethasone, 6 mg. PO, q8h) can lead to objective remissions averaging around three months' duration, in about 30 percent of women with metastatic breast carcinoma. This treatment is seldom indicated in the primary management of metastases, since chronic administration leads to Cushing's syndrome and its multiple complications. Corticosteroids are often useful in treating critically ill patients as an adjunct to radiation therapy of cerebral metastases, to cytotoxic chemotherapy of advanced pulmonary or liver metastases, and to the management of hypercalcemia. Chronic corticosteroid replacement therapy for the suppression of adrenal function may occasionally induce remis-

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### Table.

**Results of Endocrine Treatment in Patients with Metastatic Breast Carcinoma**

| Treatment     | Percent Response | Duration of Remissions (Months) | Patient's Status         |
|---------------|------------------|--------------------------------|--------------------------|
| Ovariectomy   | 40               | 12                             | Premenopausal            |
| Hypophysectomy| 46               | 18                             | Postmenopausal           |
| Adrenalectomy | 40               | 12                             | Postmenopausal           |
| Estrogens     | 35               | 12                             | 5+ years postmenopausal  |
| Progestins    | 30               | 8                              | Postmenopausal           |
| Androgens     | 20               | 6                              | Postmenopausal           |
| Corticoids    | 30               | 3                              | Postmenopausal           |
sions, but it is not as effective as adrenalectomy or hypophysectomy.

A combination of pharmacological doses of steroids is usually not indicated, although combining estrogen and progestins in postmenopausal women may produce somewhat better results than the use of estrogen alone.

**Experimental Endocrine Therapy**

Drugs have been sought to suppress or interfere with the secretion of hormones, such as estrogens, prolactin and growth hormone, as possible substitutes for endocrine ablative procedures, which are currently in limited use.

**Anti-estrogens**

Estrogens in physiological doses have been shown to accelerate the growth of some human breast cancers. This effect may be due to a direct action of the hormone on the tumor cell, since estrogen receptors have been found in about 60 percent of these cancers. The beneficial effects of ovariectomy and adrenalectomy have been attributed, at least in part, to the lowering of circulating estrogen levels in the patient. Potent, non-steroidal anti-estrogens such as Nafoxidine and Tamoxifen have been found, and apparently act by competitive binding to the estrogen receptor. Clinical trials of these agents have shown that they can induce remissions in patients with metastatic breast cancer. In a consecutive, selected series of women with Stage IV breast cancer, Tamoxifen (20 mg. PO, q12h) induced objective remissions in 45 percent of the patients. These remissions have averaged 10+ months, with the majority of patients still in remission. This drug has minimal side-effects. Tamoxifen is a useful anti-tumor agent, but further studies are necessary to compare its effectiveness with ablative procedures such as ovariectomy, adrenalectomy and hypophysectomy.

**Prolactin Inhibitors**

Prolactin plays an important role in the genesis and maintenance of growth of mammary cancer in a rat model system. The superior results of hypophysectomy and the finding of prolactin receptors in some human breast cancers suggest that the hormone may also play a significant role in human breast cancer. Drugs that suppress the secretion of prolactin, such as L-DOPA, have been studied. A clinical trial of L-DOPA (2 gm. PO, daily in divided doses) in 12 consecutive, selected patients with metastatic breast cancer produced objective tumor regression in three patients, lasting about six months. However, those patients who
responded to L-DOPA, and some who did not, obtained more effective palliation with other modalities of endocrine therapy. Measurement of serum prolactin levels in these patients revealed that L-DOPA failed to maintain suppression of serum prolactin levels during chronic administration, even when the drug was given at frequent intervals throughout the day and night. Thus, L-DOPA does not appear to be an effective agent either in the chronic suppression of prolactin secretion or as a single agent in the management of metastases.

Certain ergot alkaloids can induce profound suppression of prolactin secretion in animals and man, such as Lergotrile mesylate and bromergocryptin. A clinical trial of Lergotrile mesylate (2 mg. PO, q6h) in 12 consecutive selected patients with metastatic breast cancer failed to induce objective tumor regression, but the disease appeared to be arrested in four patients for an average of about six months. Serum prolactin levels were suppressed to one ng./ml. or less in these patients throughout the day and night. Thus, suppression of prolactin secretion alone does not appear to be a promising therapeutic modality. However, human growth hormone, known to have lactogenic activity, is not suppressed during the administration of Lergotrile mesylate; study of agents to suppress the secretion of growth hormone would be of interest. The combination of prolactin suppression with anti-estrogen administration for possible enhancement of therapeutic results is being evaluated.

Suppression of Adrenocortical Function
Aminoglutethimide can inhibit the biosynthesis of adrenocortical steroids. Richard Santen and colleagues at the University of Pennsylvania have used aminoglutethimide in combination with hydrocortisone to suppress compensatory pituitary corticotrophin secretion, in an attempt to induce a "medical adrenalectomy." They demonstrated significant suppression of steroid production with the appropriate combination of these two agents and have obtained objective tumor regression in some patients with metastatic breast cancer. Further studies are underway to demonstrate the effectiveness and practicality of this therapy compared to surgical adrenalectomy.

The Role of Cytotoxic Chemotherapy
Cytotoxic drugs such as alkylating agents, 5-fluorouracil, methotrexate and vincristine, when used as single agents produce worthwhile remissions lasting an average of about six months, in less than 20 percent of patients. However, combined use of these agents has yielded significantly better results. A five-drug combination of prednisone, cyclophosphamide, 5-fluorouracil, methotrexate and vincristine introduced by Richard Cooper of the University of Buffalo, induced objective remissions averaging around nine months duration, in about 65 percent of patients. Similar results were found in patients who initially responded to hypophysectomy and then relapsed, as compared to those who did not benefit from hypophysectomy. Combined chemotherapy may be associated with considerable morbidity and some mortality, and should be managed by physicians who are experienced in the use of these agents.

Adriamycin, as a single agent, has induced objective remissions in about 35 percent of patients in our study, who were previously treated with five-drug chemotherapy. The remissions have averaged about six months in duration.

We recommend combined cytotoxic chemotherapy as the initial treatment of choice in patients with tumors having undetectable estrogen receptors. It is also the preferred initial treatment in patients who have metastases to the liver or lungs and are poor surgical risks for endocrine ablative procedures. Patients
who respond to chemotherapy may later undergo endocrine therapy with successful results. Combined chemotherapy is also indicated both for premenopausal patients who do not benefit from ovariectomy and postmenopausal women who do not improve after hypophysectomy. Adriamycin is used when five-drug chemotherapy fails or is no longer effective.

Combined endocrine treatment and cytotoxic chemotherapy compared to the sequential use of these modalities is now being studied to determine whether longer periods of remission can be obtained in these patients.

Early vs. Late Systemic Treatment
The possibility that systemic endocrine treatment, cytotoxic chemotherapy and immunotherapy administered early might yield better results than when carried out in the advanced stage of disease is under intensive study. Reports of animal model systems have shown that systemic treatment is more effective when metastases are microscopic than when gross tumors are present. Results of surgical castration in premenopausal women with Stage I and Stage II breast cancer performed at the time of mastectomy, rather than after recurrence has developed, have yielded equivocal results. A prospective, randomized study of the effects of early versus late radiation castration in a series of premenopausal women with Stage I breast cancer, selected for favorable prognosis, has been reported by R. Nissen-Meyer of Oslo, Norway. After 13 years of observation, 85 percent of the women who underwent early castration were free of detectable disease, whereas 65 percent of those who did not undergo early castration were without detectable recurrence. This difference was statistically significant, although total survival was not significantly different in the two groups of patients after 13 years. A further period of observation is necessary to determine if early castration in premenopausal patients increases the total survival rate.

Preliminary reports on the use of cytotoxic chemotherapy immediately after mastectomy have indicated that the recurrence rate is at least delayed in patients with Stage II breast cancer. A prospective, randomized study of the effects of L-phenylalamine mustard given intermittently for a two-year period after mastectomy, versus no treatment, has been reported by Bernard Fisher and his colleagues at the University of Pittsburgh. After 18 months of observation, the recurrence rate is significantly less in the treated premenopausal group of patients. Gianni Bonnadonna of Milan, Italy reported a similar study in which three cytotoxic drugs (cyclophosphamide, 5-fluorouracil and methotrexate) were administered for one year after mastectomy; the controls received no treatment. After two years of observation, there is a significant decrease in recurrence rate in the treated group of patients. Data on the subsequent results of these studies will be anticipated with interest. Currently, there is no evidence to indicate that patients undergoing early systemic treatment of breast cancer survive longer than those who receive the same treatment at the time of first recurrence. However, the potential of early treatment is provocative, and patients with breast cancer should be encouraged to enter carefully planned study programs whenever possible.