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Journal Title: Cancer treatment reviews

Volume: 2 or 3 **Issue:**
Month/Year: 1975
Pages: 129-135

Article Author: Segaloft A.

Article Title: Hormonal therapy of breast cancer.

Imprint:

Received: **9/30/2009 02:51:56 PM**

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Cancer Treatment Reviews (1975) **2**, 129–135

Hormonal therapy of breast cancer

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Breast cancer continues to be a major neoplastic problem in our urban, Western civilization. While we are fostering increasing efforts at finding the disease early and, hopefully, in its curative stage, the economic and social forces of our civilization are setting the stage for a continuing increase in the incidence of breast cancer. Epidemiologic studies (24) indicate that bearing a child at an early age confers significant protection against breast cancer, but in our present society there is an increasing number of late marriages and decisions to have one's first child late or not to have any children. It would thus appear that if we can identify the factor, probably hormonal, responsible for the protective effect of early pregnancy and administer it appropriately for a nine-month period to young women, we may be able to use hormones to decrease the number of women who will develop breast cancers.

The next stage when hormonal therapy could be indicated is as adjuvant therapy at the time of primary treatment of clinical breast cancer, particularly in high-risk patients when their tumor burden is at its nadir. However, the prospective randomized study of castration in such patients carried out by the National Surgical Adjuvant Project (17) failed to show any advantage of surgical castration in this situation. The future may not be as gloomy, however, since there is a growing body of evidence, reviewed at the recent workshop on cytoplasmic estrogen receptors (5), indicating that the presence of a high titre of cytoplasmic estrogen receptor in the cancer may serve as a marker to identify the hormone-sensitive breast cancers which would potentially respond to castration. It will be some time before double-blind prospective studies can be carried out to identify this marker as an adequate basis for patient selection for adjuvant castration or hormone administration, but it does offer a note of optimism for early identification of potentially responsive cancers.

Much refinement of techniques and development of facilities will be required before this could be broadly applied to the more than 90,000 new breast cancers now seen yearly in the United States. Much work is being done in this area. The workshop indicated that knowledge of the cytoplasmic estrogen receptor from the primary tumor may also be useful for the future choice of therapy since, in general, metastatic lesions seem either to contain or not contain such estrogen receptors as is the case for the primary tumor.

Present indications are that more postmenopausal women have measurable levels of estrogen receptor than younger women. It is of great interest that such older women are also more responsive to hormonal therapy.

We are still faced with many women who come to us already having clinically apparent distant disease or who come in with recurrence after a variable "free period" following primary treatment. The menstrual status of these patients makes a substantial difference in our choice of therapy.

It is generally agreed that for women who are still having menstrual cycles castration, either by oophorectomy or by adequate radiation therapy, is the treatment of first choice. Beatson, the Glasgow surgeon who introduced the use of castration for advanced breast cancer, believed that the objective regressions in the cancers which he saw were associated not only with castration, but with the administration of thyroid substance to most of the patients who sustained the objective regression (2). This thesis has been tested by the Cooperative Breast Cancer Group in a prospective, randomized, double-blind study of 218 patients where either a placebo or thyroid U.S.P. was given as adjuvant therapy to castration (16). They found that there was no significant difference in objective regression rates or survival time between these two groups of patients. This study was randomized into groups based on the dominant site of metastasis. For the purpose of the above study women who were less than 1 year since their last menstrual period were considered as still menstruants. The overall remission rate was 26.6% utilizing the standard criteria of the Cooperative Breast Cancer Group (21). The mean age, the mean duration of disease and the median "free interval" did not differ significantly between the patients showing objective response and those not showing response. This study illustrates a finding that appears to be consistent in all the studies involving hormonal alterations as therapy for advanced breast cancer; namely, that the patients sustaining an objective regression survive significantly longer than those patients who do not have an objective regression. This "vacation from death" appears to be independent of the subsequent therapy given upon reactivation of the clinical disease.

Here again it is to be hoped that determinations of the cytoplasmic estrogen receptor may assist in the selection of the best candidates for castration.

Our knowledge of this biochemical material and its possible rôle in estrogen function has given us a tool which has led to the development of substances with little hormonal activity which, however, interfere with the ability of the cytoplasmic receptor to bind estradiol-17β. Preliminary evidence for some of these materials (antiestrogens) is available showing some antitumor activity in postmenopausal women with metastatic breast cancer. We hope that either the present substances or new substances with greater affinity for the estrogen receptor will enable us to substitute them for oophorectomy, since the estrogen deprivation associated with the administration of these compounds is reversible with their discontinuation.

Thus far, none of the "antiestrogens" which have been developed have this property exclusively. All the known effective agents have other endocrinologic properties in addition to the ability to interfere with the cytoplasmic binding of estradiol-17β. The steroidal antiestrogen which has been studied and reported on clinically is 2α,3α-epithio-5α-androstan-17β-ol (Shionogi 10275-S, NSC 194684). This compound was synthesized by the Shionogi Company and studied by the Japanese Cooperative Group for Hormonal Treatment of Breast Cancer, using the techniques, randomization and extramural review pioneered by the Cooperative Breast Cancer Group in the United States. This compound was studied in a prospective, double-blind, randomized study against testosterone pro-

pionate since it is androgenic as well as antiestrogenic. The results have been published (13). They demonstrated a difference in objective regression rate between the two compounds and a substantially lesser incidence of virilization in the patients receiving the antiestrogen. The antiestrogenic-treated group had a 29% objective regression rate and the testosterone propionate-treated group 18%.

Non-steroidal antiestrogens have been studied clinically, two of them substituted triphenylethylene derivatives which in high-dose levels have estrogenic properties rather than antiestrogenic properties. At the present time it is not certain whether this estrogenic property is due to their conversion to phenolic derivatives. The first of these, Nafoxidine (U-11, 100A, NSC 70735), was studied by the European Breast Cancer Group (6) and reported as capable of producing objective regression in postmenopausal women with advanced breast cancer. However, a wide variety of dosages was employed and it is not clear whether the most effective dosages were estrogenic or antiestrogenic in the hosts. The compound has shown unpleasant side effects, the most annoying of which is the development of photosensitivity.

The other compound, Tamoxifen (ICI 46, 474, NSC 180973), is known as the *trans* isomer, the *cis* isomer being basically estrogenic. (There is some difference among chemists as to the interpretation of the physical data on these isomers. The American chemists refer to the antiestrogenic isomer as the *cis* isomer. For example, the antiestrogenic isomer of clomiphene, also a substituted triphenylethylene, is known as cisclomiphene and the estrogenic isomer is known as transclomiphene. The clomiphene available for use as an ovulatory stimulant is a mixture of the two isomers.) This compound has been employed extensively in Great Britain. We are not aware of any prospective, randomized, double-blind studies. However, on the basis of studies which have been done, the compound is commercially available in Great Britain at the recommended oral dosage level of 20 mg per day.

It should be realized that the ovary is not only the source of estrogen but of various progestational and androgenic substances as well as relaxin, all of which may play a rôle in the growth of established breast cancers.

We have known for some time that the greater the postmenopausal age of the patient with advanced breast cancer the greater the chance of local or visceral lesions responding to alterations in the hormonal milieu, either by administration of hormonal therapy or by ablative therapy such as adrenalectomy or hypophysectomy. It is encouraging to see the data presented at the estrogen receptor workshop which indicate that with increasing age there is an increase in the percentage of patients whose tumors show the receptor as well as an increase in the level of receptor. Although some have thought that older women respond best to estrogens and younger women respond best to androgens, as will be discussed below, this has not been borne out by modern prospective, randomized studies. The dominant sites of involvement with metastatic breast cancer also have a distinct effect on the objective regression rate with hormonal administration. The highest regression rates are seen with local recurrences, soft tissue or lymph-node disease, while the poorest regression rates are observed for dominantly visceral disease; osseous metastases occupy an intermediate position. Thus it should be apparent, as we will point out for specific studies, that the greatest regression rates are seen with local disease in elderly women.

In addition to the direct production of tumor regression certain hormonal agents have effects which are sufficiently useful to play an important rôle in all types of treatment of advanced breast cancer. For example, in a patient with brain metastases and a neurologic deficit, the administration of ample amounts of corticosteroids can reduce the neurologic

deficit and brain edema sufficiently to permit adequate and useful administration of radiation therapy. Corticosteroids are also very active in the treatment of the resistant hypercalcemia which often characterizes advancing breast cancer. The administration of androgenic hormones not only has the desired primary effect of producing objective regression of advanced breast cancer but androgens are frequently useful in the stimulation of the production of formed elements of the blood, particularly erythrocytes and, as most recently reported, platelets (7, 14). Corticosteroid therapy is also of assistance in the management of the jaundice due to hepatic metastases and the dyspnea associated with lung metastases.

Corticosteroids have been administered with the idea of inhibiting the production of ACTH and reducing adrenal function to the point where it could be called a medical adrenalectomy. Although a wide variety of objective regressions have been claimed for the administration of corticosteroids with this function, our own experience has been that a greater number of objective regressions is seen when active corticoids are combined with the administration of thyroid substance. This was reported early by Lemon (15) and by Gardner and associates (8). The newer corticosteroids appear to have no advantage other than their usual reduction in some of the distressing "side-effects".

Another development in hormonal therapy has been the synthesis of various compounds which have fewer of the unpleasant hormonal effects, erroneously called side-effects, while still retaining the anti-tumor activity. The undesired effects of estrogens are, particularly, nausea, vomiting and stress incontinence, while those of androgens are virilization with its hirsutism, plethoric appearance and sometimes markedly increased libido.

The classical androgen for the treatment of advanced breast cancer is testosterone propionate, generally administered intramuscularly as 100 mg thrice weekly. It has been the custom to avoid the use of long-acting esters of testosterone in the treatment of breast cancer because they make it impossible to discontinue therapy in those unusual patients in whom hypercalcemia is precipitated by the administration of testosterone.

A summary of the results of the use of testosterone propionate in a series of prospective, randomized, generally double-blind studies has been published by the Cooperative Breast Cancer Group (9). Here it has been found that those patients experiencing objective regression on therapy also experience better survival than those patients failing to achieve objective regression regardless of the treatment of the reactivated disease.

As one would expect, the testosterone-treated patients show the physiologic effects of long-term administration of a potent androgen and are virilized, having hirsutism, weight gain with increase in muscle mass, clitoral enlargement, hoarseness, acne and plethora. Many of the patients also had increased libido sufficiently distressing so that they were unwilling to go on with therapy, often in the face of excellent objective regressions.

Lesions of all organs respond to testosterone therapy.

The parenteral administration of hormones is not always readily accomplished and since potent oral androgens are available these have been employed as substitutes for parenteral therapy. The typical androgen for this use is methyltestosterone (NSC 9701), generally used in a dose of 200 mg per day by mouth. Methyltestosterone has essentially the same pattern of regression induction and virilizing potential as testosterone propionate. However, in addition it has the property common to 17-alkyl steroids, namely, an interference with the excretory function of the liver sufficient to produce jaundice and occasionally substantial hepatic damage. Methyltestosterone also shares with testosterone propionate the ability to reduce gonad-stimulating hormones in the urine (20). It does not increase the urinary 17-ketosteroids but gives rise to a series of 17-methylated metabolites (18, 19).

The first of the less androgenic compounds, 2α-methyl-5α-dihydrotestosterone propionate (Dromostanolone, NSC 12198), was introduced by the studies of the Cooperative Breast Cancer Group. This compound appears to have essentially the same pattern of response as testosterone propionate but is significantly less virilizing and less able to decrease the urinary gonad-stimulating hormones. Studies by the Cooperative Breast Cancer Group have indicated that the optimal dose of this androgen is 100 mg thrice weekly IM. It is commercially available in the United States under the trade name of Drolban® (3, 23).

The ultimate reduction of androgenic activity, indeed the complete destruction of hormonal activity, was seen with the introduction of Δ^1-testololactone (Teslac®, NSC 23759) (22). This compound is an androgenic derivative devoid of all discernible hormonal activity which has been carefully studied by the Cooperative Breast Cancer Group. Prospective, randomized, double-blind studies have indicated that the optimal dose of this steroid is 1 g per day by mouth. Unfortunately there has been a somewhat lower objective response rate seen with this extremely well-tolerated androgen derivative (25).

An additional oral androgen with greatly lessened androgenicity and hepatic toxicity, 17β-hydroxy-7β,17-dimethylandrost-4-en-3-one (NSC 88536, Calusterone, Methosarb®), has also been introduced as the result of prospective, randomized, double-blind studies by the Cooperative Breast Cancer Group. The initial studies reported indicate a 28% objective response rate as compared to an 18% objective response rate with one gram per day of Δ^1-testololactone (10).

This compound has been reported as showing an additional very interesting property; namely, the capability of increasing the platelet counts in patients where such counts are depressed. Extensive confirmation of this property may make this compound particularly promising as an adjuvant for chemotherapy in breast cancer (12).

The largest class of hormones which have been administered are estrogens. The initial stimulus to the study of estrogen administration was the availability of synthetic, reasonably priced non-steroidal estrogens, particularly diethylstilbestrol. This has been the cornerstone of estrogen therapy of advanced breast cancer since its introduction.

There are not a great many trials of administrative estrogenic hormone therapy for comparison but the most commonly employed dosage of diethylstilbestrol has been 15 mg per day orally. It would appear, as noted above, that elderly women with soft-tissue disease are, as with androgens, the best candidates for objective regression with diethylstilbestrol administration.

As opposed to the success in developing androgens with lesser androgenic activity still active against breast cancer, we are not aware of any such estrogen derivatives. There appears to be little choice between the various estrogens as long as they are given in equivalent activity.

The hormonal consequences of large doses of estrogenic material are, as mentioned above, nausea, vomiting, breast soreness, pigmentation (particularly of the nipples and sometimes of the face), episodic bleeding if the uterus is present, sometimes excessive cervical and vaginal secretions and, most uncomfortable to many women, the problem of stress incontinence. On the whole, most women tolerate the estrogen therapy quite well and the nausea and vomiting, in particular, can be prevented either by gradually escalating the dose over a period of some weeks or giving the entire dosage by mouth together with a long-acting antinauseant before bedtime. One of the other consequences of estrogen therapy is the retention of fluid and electrolytes. This can result in congestive heart failure in susceptible patients and may require the use of diuretics and, occasionally, digitilization.

The Cooperative Breast Cancer Group has tested dosages of diethylstilbestrol up to 1500 mg per day and found the best regression rate with this highest dose, but also the greatest number of dropouts. They are proposing that it may be possible to induce remissions with larger doses and maintain remissons with other means.

The other type of hormonal therapy is the removal of endocrine glands to eliminate the source of hormones which might be sustaining the growth of the tumor. We have already referred above to the successful use of castration in appropriate menstruating women but in our present day with currently available techniques it has proven feasible to remove the adrenals and/or the pituitary as well. Both of these procedures do have reasonable regression rates in advanced breast cancer, and with our presently available drugs the maintenance of such patients is not an insurmountable task requiring care in a large medical center.

It does appear that if adrenalectomy is done earlier in the course of the metastatic disease the objective regression rate is higher. However, the survival of the patients and the duration of the regressions are not equivalently improved (4).

Finally, as with the antiestrogens, we are developing pharmacologic means of "endocrine ablation". L-Dopa and certain ergot derivatives are capable of reducing circulating levels of pituitary prolactin and have been reported also as producing regressions in advanced breast cancer. Aminoglutethimide and other compounds can produce reductions in adrenal secretions, but as yet most of these trials have not been complete enough to have a sufficient literature to be able to report adequate tumor-response rates.

While progestational agents have the best record and are the agents of choice for treatment of metastatic adenocarcinoma of the endometrium, their results have not been as salutary in the treatment of advanced breast cancer. While the present orally active progestational agents are well tolerated and do not have the local irritating effects of progesterone itself, the objective regression rates obtained do not presently enable us to recommend them as the first-line hormonal agents for the therapy of advanced breast cancer (11).

The most recent progestationally active compound to come into wide use is megestrol acetate, which has been reported to produce 23% of objective regressions when given late in the course of treatment of advanced breast cancer (1). The advantage of such progestational agents is that they seem to be refreshingly free of untoward side-effects.

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