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Perspectives and Commentaries

Hormone-induced Tumor Flare

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IT HAS been known for almost a century that some human breast cancers depend on steroid sex hormones for their continued proliferation. Based on his belief that the prognosis was worse in younger women, Schinzinger wondered in 1889 "whether it would be permissible to make the ladies old more quickly by removing their ovaries ... ". Unaware of this suggestion Beatson performed the first bilateral oophorectomies in 1895 for advanced breast cancer in two premenopausal women and described significant regression of the primary tumor in both patients. As a young physician he had learned from farmers the effects of the ovaries on lactation. Furthermore, he had compared the histological changes in the lactating breast after pregnancy with those seen in carcinoma, since the proliferation of generations of epithelial cells is common to both conditions. He laid the foundation for the hormone manipulative therapy in the treatment of human breast cancer. In the late 1930s estrogens were discovered and used in the belief that they would stimulate breast cancer and render it more sensitive to radiation or colchicine. Contrary to expectation, regressions were noted. This is probably how additive hormonal therapy for breast cancer began. Subsequent studies revealed that physiological amounts of a hormone might stimulate tumor growth, whereas pharmacological doses of the same hormone could inhibit growth of the tumor.

In 1984 the oncologist can select additive (estrogens, androgens, progestins, glucocorticoids), ablative (oophorectomy, adrenalectomy, hypophysectomy), competitive (antiestrogen, antiandrogen) or inhibitory (aminoglutethimide, testolactone, trilostane, buserelin, leuprolide) hormonal therapies. The latter have made major surgical ablative procedures such as hypophysectomy and adrenalectomy largely redundant. The overall response rate to hormone therapies is approximately 30% in unselected patients but 60% in estrogen receptor (ER)-positive tumors, while ER-negative tumors are much less likely (10%) to respond. Other receptor measurements, especially of progesterone receptor, further improve predictive accuracy for hormone treatment.

While it is the purpose of hormone manipulations to alter the endocrinological milieu in such a way as to induce tumor regressions, it has been observed in the clinic that in some cases tumor stimulation ('tumor flare') seems to result. This term has been applied to three different manifestations occurring soon after the institution of hormone therapy [1, 2]. The first is an increase in swelling, erythema, itching or pain in soft tissue metastases of breast cancer or the development of new lesions; the second is an increase in skeletal pain in patients with bone metastases, sometimes severe enough to induce the treating physician to withdraw the agent prematurely; the third is the onset of hypercalcemia. This occurs most often in patients with widespread bone metastases, especially osteolytic or mixed lesions, but it can be seen sometimes in patients with osteoblastic metastases or even in patients with occult bone involvement. The rapid onset leads to the characteristic gastrointestinal and neurological symptoms of the hypercalcemic syndrome, which can be fatal if not recognized and treated promptly.

Evidence suggesting 'tumor flare' usually occurs within 2-21 days following initiation of hormone therapy. Tumor flare has been reported most commonly following the administration of estrogens (1%) [1], androgens (3%) [1] and tamoxifen (2.2%) [3]. It is very rare with progestins [4, 5] and ablative surgery, and to our knowledge has not been reported for aminoglutethimide. The incidence of hypercalcemia induced by

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hormone therapy is more difficult to ascertain in view of the high incidence of spontaneous hypercalcemia in metastatic breast cancer (12–15%) [1]. It has been reported in 5% of estrogen- [1], 11% of androgen- [1] and 1.2% of tamoxifen-treated [3] patients, with higher percentages for patients with skeletal metastases [6].

So-called tumor flare can represent one of three possible tumor evolutions. The first may be no more than the continuing rapid progression of a relatively severe disease, resistant to hormone therapy. The second is an initial apparent acceleration of disease, ultimately followed by a tumor response which occurs in spite of continued therapy or following a brief interruption. The third is a genuine tumor growth enhancement induced by the hormone therapy. It may be very difficult or impossible to determine the eventual outcome during the first few days. Only accurate serial measurements of tumor volume before and after initiating treatment can clarify the final outcome. True acceleration is proven only if the growth rate increases as long as the treatment is continued and then decreases after it is stopped. This has rarely been the case for tamoxifen [7]. In most cases tumor flare or hypercalcemia has meant that the tumor is hormone-sensitive and a tumor regression has ensued with continued treatment.

The occurrence of true tumor stimulation is rare with the hormonal preparations now commonly used (tamoxifen, medroxyprogesterone acetate, megestrol).

However, it is important that the clinician is aware of this possibility. If the patient develops signs of tumor flare, hormone treatment may be continued or temporarily reduced unless skeletal pains are excessive, or in the case of severe hypercalcemia. The latter should be treated with the usual measures (saline hydration, diuretics, corticosteroids, calcium deprivation, calcitonin, etc.). Hormonal treatment may be resumed (after 1–3 weeks), if necessary temporarily at a lower dosage, except in the rare case of well-documented sustained tumor growth acceleration.

Although hormone treatments have well-documented activity in about one-third of patients with advanced breast cancer, not much is known about their mechanism of action. The subject is complex. It is a poorly understood paradox that at physiological doses estrogens stimulate breast cancer growth in experimental animals and probably in women, whereas tumor regressions are obtained at pharmacological doses. It is equally paradoxical that patients who have responded to pharmacological doses of estrogens may subsequently respond to the removal of estrogens. Some hormones bind not only to their respective receptors but also to those of other hormones; furthermore, they can influence the synthesis and thus the concentration of receptors. Hormones can be administered in sequence to exploit this phenomenon therapeutically. Estrogens or tamoxifen induce a progesterone receptor response; this can be followed by a progestin at the peak of progesterone receptor induction [8]. Pharmacological doses of estrogens may inhibit synthesis of the estrogen receptor and thus impede the entry of the hormone into the cell nucleus. Antiestrogens not only block the uptake of estrogen by target tissues but also cause depletion of estrogen receptor. Progestins bind not only to progesterone receptors but also to androgen- and glucocorticoid receptors and they act as antiestrogens possibly by depletion of estrogen receptors.

The concentration of one hormone may affect the concentrations of other hormones, e.g. progestins can decrease the amount of estrogen available due to acceleration of estrogen catabolism. One hormone may be converted to another, e.g. some androgens can be converted into estrogens by aromatization in adipose tissue and breast tumors. In some patients some progestins may be converted to estrogens. Progestins may decrease the conversion of androgen into estrogen. Furthermore, various metabolites of hormones may have biologic activity.

Hormones influence the function of other endocrine organs. Progestins inhibit the pituitary function as they suppress the release of gonadotrophins, ACTH and growth hormone. A possible mechanism of action of androgens in premenopausal women with breast cancer is the suppression of gonadotrophin production with a resultant decrease in ovarian function. Following oophorectomy the persistence of estrogens is due to the conversion of androgens of adrenal origin to estrone in peripheral tissues and breast cancer tissue.

Some hormonal agents may have variable effects depending on the dosage or the species. This interspecies difference in the response of the same end organ has been a striking feature of the pharmacology of tamoxifen. There is a spectrum of activity which ranges from pure agonist to full estrogen antagonist. This brings into question the relevance of some of the animal data for the clinic. It has been proposed by Veldhuis and Santen [9] and documented by Reddel and Sutherland [10] that tamoxifen may, under certain circumstances, exert a biphasic action. Initially, at low concentration, it acts as a weak estrogen agonist, and later, as its concentration increases with prolonged treatment, as an

estrogen antagonist. This could account for the uncommon phenomenon of tamoxifen-induced flare and the remission with continued treatment in some patients. It is evident that hormonal manipulations have complex biological effects on tumor growth and regression. Thus it should not be surprising that under certain rare circumstances tumor stimulation occurs instead of the expected regression.

Future research will undoubtedly provide a better understanding of the role of hormones in the etiology and development of breast cancer and their mechanism of antitumor action. The susceptibility of individual breast cancers, and thus the selection of endocrine therapy, will be improved by receptor determinations and *in vitro* sensitivity testing techniques. Additive hormone therapy is becoming more specific and almost devoid of significant side-effects. New molecules with pure antagonist activity will be developed. Surgical ablative procedures, which are very crude ways of inhibiting the secretion of a particular hormone, have been supplanted by pharmacologic means of hormonal suppression.

Endocrine therapy remains a significant weapon in the armamentarium for the treatment of advanced breast cancer. Furthermore, attempts are being made to combine endocrine treatment and chemotherapy to advantage based on the principle of estrogenic synchronization of the cell cycle of hormone-dependent cells. Cytotoxic drugs predominantly kill cells engaged in the mitotic cycle. Thus a brief estrogenic exposure should stimulate cell division and might therefore amplify the killing effect of cytotoxic drugs administered shortly thereafter [11, 12].

REFERENCES

1. Stoll BA. *Endocrine Therapy in Malignant Disease.* London, W. B. Saunders, 1972.
2. Plotkin D, Lechner JJ, Jung WE, Rosen PJ. Tamoxifen flare in advanced breast cancer. *JAMA* 1978, **240,** 2644-2646.
3. Patterson J, Furr B, Wakeling A, Battersby L. The biology and physiology of 'Nolvadex' (tamoxifen) in the treatment of breast cancer. *Breast Cancer Res Treat* 1982, **2,** 363-374.
4. Bernheim JL, Callewaerts W, Paridaens R, Roobol C. Human mammary tumor growth promotion by medroxyprogesterone acetate in tumor stem cell clonogenic assay. *Cancer Treat Rep* 1983, **67,** 101-102.
5. Greenwald ES. Megestrol acetate flare. *Cancer Treat Rep* 1983, **67,** 405.
6. Legha SS, Powell K, Buzdar AU, Blumenschein GR. Tamoxifen-induced hypercalcemia in breast cancer. *Cancer* 1981, **47,** 2803-2806.
7. Legault-Poisson S, Jolivet J, Poisson R, Beretta-Piccoli M, Band PR. Tamoxifen-induced tumor stimulation and withdrawal response. *Cancer Treat Rep* 1979, **63,** 1839-1841.
8. Pelligrini A, Massidda B, Mascia V *et al.* Ethinyl estradiol and medroxyprogesterone treatment in advanced breast cancer: a pilot study. *Cancer Treat Rep* 1981, **65,** 135-136.
9. Veldhuis JD, Santen RJ. Tamoxifen flare. *JAMA* 1979, **241,** 2506-2507.
10. Reddel RR, Sutherland RL. Tamoxifen stimulation of human breast cancer cell proliferation *in vitro:* a possible model for tamoxifen tumour flare. *Eur J Cancer Clin Oncol* 1984, **20,** 1419-1424.
11. Paridaens R, Blonk van der Wijst J, Julien JP *et al.* Medical adrenalectomy and cyclic chemotherapy preceded by estrogenic recruitment in advanced breast cancer. A phase II trial of the EORTC Breast Cancer Cooperative Group. *Proc ASCO* 1984, **3,** 130 (Abstr. c-508).
12. Lippman ME, Cassidy J, Wesley M, Young RC. A randomized attempt to increase the efficacy of cytotoxic chemotherapy in metastatic breast cancer by hormonal synchronization. *J Clin Oncol* 1984, **2,** 28-36.