Cancer-50 Years Later

Taylor SG III, Slaughter DP, Smejkal W, Fowler EF, Preston FW. The effect of sex hormones on advanced carcinoma of the breast. *Cancer* 1948;1:604–17.

Progress in Endocrine Therapy for Breast Carcinoma

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Our understanding of the mechanisms of action of hormonal agents in normal and pathologic breast tissue has expanded dramatically over the last 30 years. The identification of specific receptors for estrogens, progestins, androgens, and glucocorticoids led to the elucidation of the cascade of events that results in the intended effect of steroid hormones.[1,2] This cascade begins with the entry of the hormone into the cell, its binding to the specific receptor protein, and the signal transduction pathway that eventually results in the intended hormonal effect, such as induction of cell proliferation or division, or the production of additional hormonal receptor proteins. The contributions of multiple investigators to this process were summarized elegantly by Levenson and Jordan in 1997.[3] The ability to identify and quantitate estrogen and progesterone receptor expression in individual tissues soon was followed by clinical correlations that established the diagnostic and predictive importance of these elements in the management of metastatic and primary breast carcinoma.[4] Thus it was shown that patients with metastatic breast carcinoma whose tumors express a high concentration of estrogen receptors have a much higher probability of response to hormonal therapy than patients whose tumors express a low concentration or do not express estrogen receptors at all. Subsequent studies demonstrated that the simultaneous expression of estrogen and progesterone receptors further increased the probability of response to endocrine therapy, thus serving as a marker of an intact hormonal effector pathway.[5] Although other clinical characteristics of the tumor such as extent of metastatic spread, patient age, duration of menopause, disease free interval, location of tumor, and, more recently, some molecular markers may influence the probability of response further, by far the degree of hormone receptor expression is the most important predictive factor.

These observations also were reproduced in the context of the primary multidisciplinary management of breast carcinoma. Thus, adjuvant hormonal therapy, mostly with the antiestrogen tamoxifen, was found to be effective in estrogen/progesterone receptor positive tumors, and essentially ineffective in those tumors without hormone receptor expression.[6–10] Hormone receptor expression also was found to be an important prognostic indicator for patients with metastatic and primary breast carcinoma.[11] Patients with hormone receptor positive tumors have a longer survival after the development of metastasis than patients with hormone receptor negative tumors.[12–16] There also is a different pattern of metastatic spread, with hormone receptor positive tumors metastasizing preferentially to soft tissues and bone, whereas hormone receptor negative tumors spread with

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greater frequency to deep visceral organs, such as the liver, lung, and brain.[17]

In primary breast carcinoma patients with estrogen receptor negative tumors tend to have earlier recurrences and, at least during the first 5 years, a higher incidence of failure than patients with hormone receptor positive tumors. Some studies with long follow-up have suggested that after the initial 3–5 years, the prognostic value of estrogen receptor expression decreases or even disappears, with the ultimate probability of recurrence and death being similar for estrogen receptor positive and estrogen receptor negative tumors, or in some cases, even inverted.[18–21]

While our biologic understanding of receptor activity has expanded, a quiet revolution was taking place in the development of hormonal agents. Perhaps the most influential group of these agents was the antiestrogens.[22] Originally developed for purposes of contraception, tamoxifen and nafoxidine were found to have potent antiestrogenic activity.[22,23] The initial clinical trials showed that approximately 33% of patients with previously untreated metastatic breast carcinoma, and perhaps a somewhat smaller percentage of patients with prior treatment, responded to antiestrogen therapy.[24] No dose response was identified, and from the very early studies it became apparent that this agent was better tolerated than all other hormonal agents available at the time. The completion of several randomized clinical trials that compared tamoxifen with estrogens,[25] aminoglutethimide,[26] progestins,[27,28] and oophorectomy[29,30] soon established the preeminent role of this agent as the treatment of choice for hormone-responsive metastatic breast carcinoma. Subsequent experience extended these observations to male breast carcinoma,[31–33] and to the management of lymph node positive[6,34,35] and lymph node negative[6,8,36,37] breast carcinoma. Today, antiestrogens in general, and tamoxifen in particular, are considered the first-line treatment of choice for hormone-responsive metastatic breast carcinoma, and hormonal receptor positive primary breast carcinoma that requires adjuvant systemic treatment.[24]

A second group of hormonal agents that was developed over the last 30 years includes the progestins.[38] Megestrol acetate[39,40] and medroxyprogesterone acetate[41,42] are the two principal representatives of this group. The mechanism of action of progestins is uncertain. Inhibition of gonadotrophin secretion and reduced steroid biosynthesis have been proposed; others have put forth a direct inhibition of cell growth after binding of ligand to the progesterone receptor, and down-regulation of estrogen receptor levels, resulting in reduced sensitivity of tumor cells to estrogen. Clinical studies have demonstrated that patients with estrogen receptor positive tumors respond better to progestins than those with estrogen receptor negative tumors. Although controversy regarding the optimal dose of progestins is ongoing, the majority of experts would agree that a dose response remains unconfirmed. Progestins are well tolerated, but cause weight gain, fluid retention, and dyspnea. For this reason, this agent usually is recommended as second-line hormone therapy after tamoxifen has outlived its usefulness.

A dramatic new development is the appearance of specific and selective aromatase inhibitors.[43–45] Aminoglutethimide was the first aromatase inhibitor developed, but this compound was not selective, resulting in broad inhibition of adrenal steroid production. In addition, substantial toxic effects also accompanied its use in a significant minority of patients with breast carcinoma. Therefore, although its equivalence to similar endocrine interventions was established by clinical trials, the appearance of better tolerated and more selective aromatase inhibitors such as anastrozole and letrozole has completely displaced aminoglutethimide. Both anastrozole and letrozole have been shown to be more effective than progestins[46] and better tolerated than aminoglutethimide. Therefore, their therapeutic ratio appears superior to the progestins and aminoglutethimide. Currently, these agents are being compared with antiestrogens in the treatment of metastatic breast carcinoma. Furthermore, future studies will determine whether the addition of selective and potent aromatase inhibitors to other hormonal interventions, such as antiestrogens or gonadotrophin-releasing hormone analogs, will result in improved therapeutic efficacy without a substantial increase in toxic effects.

The earliest randomized trials of antiestrogens determined that these compounds were equivalent to the major surgical ablative procedures (oophorectomy, adrenalectomy, and hypophysectomy) without the irreversible effects of the surgical procedures.[47,48] These results rapidly transformed the face of hormonal therapy, causing the total displacement of the major surgical ablations. Although ovarian ablation still is employed in some centers for reasons of cost and expediency, hormonal approaches with better therapeutic ratios are preferred.[1]

The luteinizing hormone-releasing hormone (LHRH) analogs were developed to inhibit the entire hypothalamic, hypophysiary, and gonadal axis.[1,49–51] These agents have proven to be of major efficacy in chemical gonadal ablation in both women and men. Therefore, they are used for the management of breast and prostate carcinoma with considerable success.

They are very well tolerated, with a side effect profile that compares favorably with the antiestrogens or the new aromatase inhibitors. Although the systems of administration still are evolving, these agents have numerous advantages over surgical or radiant gonadal ablation.

Although high dose estrogens seldom are used, synthetic androgens (fluoxymesterone) are used in patients with persistently hormone-responsive tumors as fourth-line therapy, after antiestrogens, aromatase inhibitors, and progestins.

New Directions in Hormonal Therapy

The existing antiestrogens (tamoxifen and toremifene) have mixed estrogen agonist and antagonist effects.[52–54] Although the antiestrogenic effect is responsible for the antitumor efficacy, the estrogen agonist effect results in maintenance of bone mineral content as well as a favorable modification of plasma lipid concentrations. However, it has been proposed that the estrogen agonist effect is responsible for the development of endometrial carcinoma,[55] and most likely for the development of antiestrogen-resistant breast carcinoma cells.[56] Recent research in antiestrogens has produced two new types of compounds. The first represent pure antiestrogens, without any agonist effects.[56] Preliminary reports suggest that these agents might be effective in tamoxifen-resistant tumors in vitro and in vivo. The long term clinical effects and the therapeutic ratio of these agents remain under investigation. The second group of agents is the selective estrogen receptor modulators (SERMs).[57,58] These agents retain the antiestrogenic effect of tamoxifen over breast carcinoma while retaining the estrogen agonist effect over bone and plasma lipids. At the same time, they are deprived of the estrogen agonist effect over the endometrium and potentially other tissues. The Food and Drug Administration recently approved the first SERM for the management of osteoporosis. Other indications under investigation include the management of metastatic breast carcinoma, adjuvant therapy of breast carcinoma, and hormone replacement therapy in patients with a history of breast or gynecologic malignancies.

Antiandrogens, antiprogestins, and additional types of aromatase inhibitors currently are under laboratory and clinical investigation.[59]

Until the late 1980s, it generally was believed that combination hormonal therapy was not more effective, but potentially more toxic than single agent hormonal manipulation. The advent of modern hormonal agents has shaken this belief. Preliminary results suggest that the addition of tamoxifen to LHRH analogs might result in increased therapeutic efficacy.[49,51] An additional evaluation of combined hormonal therapy, both simultaneously and in sequence, clearly is warranted.[60]

There are indications that mutations in the p53 gene, the overexpression of HER-2/*neu* oncogene, and other well characterized molecular abnormalities might be associated with resistance to hormonal intervention.[61–63] If these findings are confirmed prospectively, they will lead to better selection of hormone-responsive and hormone-resistant patients for optimal therapy, and might also provide novel targets for the prevention or reversal of hormonal resistance.

The article by Taylor et al.[64] represents a classic example of enlightened empiricism. At a time when modern clinical trial methodology was unknown, and when oncology itself was just a nascent discipline, these pioneers provided an incredible lesson in the power of careful clinical observation. All their critical observations have been confirmed by subsequent studies, including the controlled randomized trials initiated several decades later. The authors reported that estrogen therapy was effective in approximately 33% of female patients. Furthermore, they observed a higher frequency of objective responses in older, postmenopausal women compared with younger women. The observation that estrogen therapy was more effective in cutaneous, subcutaneous, and lymph node metastases compared with visceral metastases also has been confirmed repeatedly. Taylor et al. also described the lack of radiographic objective responses in osseous metastases, which is more an artifact of our ability to monitor bone resorption and remodeling than a true lack of therapeutic efficacy of the hormones under study. Taylor et al. made similar observations regarding androgen therapy. However, with the use of androgens, they provided clear evidence of recalcification in bone metastases, a reproducible effect with particular relevance to androgen treatment. The authors also demonstrated response to androgens in estrogen receptor-resistant tumors, and documented the rapid relief of pain in patients with bone metastases. The phenomenon of androgen-induced tumor flare also was described in this report. The authors further observed that the duration of response to hormonal therapy was dependent on the duration of administration of hormones, and that when metastatic tumors recurred after discontinuation of hormonal treatment, reinduction was possible with the same agent. Taylor et al. reported the appearance of mixed responses. Other important observations included the fact that hormonal

therapy could down-stage inoperable locally advanced breast carcinoma patients and convert them into surgical candidates. The authors also reported a single case of male breast carcinoma with a dramatic response to hormonal therapy. Taylor et al. presented one of the earliest reports of what appears to be an objective response to testosterone in a patient with brain metastasis. Finally, the authors presented a very careful analysis of the side effects and toxicity of both estrogens and androgens in this group of patients with breast carcinoma. Their list is complete enough that more recent controlled trials have not added many new items to it.

The lesson from this article is that with commitment and dedication, careful clinical observation has an extremely important role in furthering our understanding of the behavior of a disease, as well as the therapeutic interventions under evaluation. Today, 50 years after the publication of this article, we are fortunate enough to have a much broader and deeper understanding of the natural history of breast carcinoma, as well as the mechanism of action of hormonal interventions. Furthermore, the last 50 years have given us an increasingly refined methodology for the planning and conduct of clinical trials, whereas a systematic approach to new drug development has provided us with novel, effective, and well tolerated hormonal agents. Although we stand on the shoulders of giants, we will look forward with optimism to additional developments in the management of primary and metastatic breast carcinoma.

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