HORMONE THERAPY
IN BREAST AND PROSTATE CANCER
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Foreword by ELWOOD V. JENSEN

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FOREWORD

It has been said that the control of disease has three goals, which, in increasing order of attraction are palliation, cure, and prevention. For most types of disseminated cancer, medical science has achieved only the first of these objectives, while for some malignancies the side effects of the therapeutic agents employed rival the disease itself in precluding a desirable quality of life. In contrast, those cancers of the breast and prostate that retain the hormone dependency of the tissue of origin, and thus are sensitive to endocrine manipulation, offer a more favorable situation for control. Hormone Therapy in Breast and Prostate Cancer takes the reader on a fascinating scientific journey that illustrates how the combination of clinical and basic investigations has realized the first two objectives for both of these prevalent malignancies and, with breast cancer, the promise of being close to the third goal.

Our endocrinological tour begins with the surgeons, who, more than a century ago, with remarkable insight at a time when estrogenic hormones were still unknown, excised the ovaries of premenopausal women with advanced breast cancer, causing tumor regression in some patients. Forty-five years later, after animal experiments had established that the growth of the prostate gland depends on androgenic hormone produced by the testes, it was shown that removal of these organs leads to striking remissions in most men with disseminated prostate cancer. Subsequently, it was found that some, but not all, postmenopausal women with metastatic breast cancer respond favorably to excision of either the pituitary or adrenal glands. For those patients with tumors of the hormone-dependent type, the remissions obtained by endocrine ablation were superior to those provided by cytotoxic chemotherapy, and, during the 1950s and 1960s, surgical removal of the sex hormone-producing organs became the standard therapeutic approach for treating advanced breast and prostatic neoplasia.

Despite the benefit derived from endocrine ablation in many patients with hitherto untreatable disease, these procedures are not perfect. Although most prostatic cancers respond to castration, only one-third of all breast cancer patients have tumors that are hormone-dependent. Thus, most patients with mammary cancer were being subjected to a non-reversible surgical procedure that did not help them. Moreover, those undergoing adrenalectomy or hypophysectomy required the continual administration of glucocorticoids for their maintenance.
As described in the chapters that follow, a combination of research in chemistry, biochemistry, physiology, and pharmacology has provided alternative approaches to the therapy of breast and prostate cancer that have eliminated most of the disadvantages associated with surgical removal of the hormone factories. Elucidation of the pathways of estrogen and androgen biosynthesis led to the discovery of compounds that block their production, and identification of substances from the pituitary that control the factories has permitted the development of antagonists of their action. The demonstration that estrogens, and later androgens, exert their stimulatory effects in combination with specific receptor proteins explained the ability of certain compounds to block hormone action at the target cell level and offered a rational means for finding improved antagonists that compete with the hormone for binding to the receptor. Finally, analysis of the estrogen receptor content of excised tumor specimens permitted the identification of those breast cancers that will not respond to either endocrine ablation or antiestrogen therapy, thus excluding the majority of patients from therapeutic procedures that will not help them.

Not only have antiestrogens replaced surgical ablation as first-line treatment for advanced breast cancer, as well as for adjuvant therapy at the time of mastectomy, but recent clinical trials indicate that certain of these agents, such as tamoxifen, that are tolerated on prolonged administration can prevent the occurrence of breast cancer, at least in high-risk individuals. Thus, for this malignancy, one seems close to achieving the third and most elusive goal of cancer control, that of prevention.

When one surveys the development of tamoxifen and related antiestrogens as therapeutic and, possibly, preventive agents for breast cancer, one is impressed by the insight, fortitude, and persistence of the scientist whom we all recognize as the father of the clinical utility of tamoxifen. This was all the more remarkable given the disastrous experience of others with the side effects of certain earlier antiestrogens. To illustrate the progress that has been made over the past thirty years, it may be appropriate to dedicate the following thought to Craig Jordan:

“\text{A lady with growth neoplastic}\
\text{Thought ablation was just a bit drastic.}\
\text{She preferred that her ill}\
\text{Could be cured with a pill,}\
\text{Which today is no longer fantastic.”}\

\textbf{Elwood V. Jensen}\
\textit{Professor Emeritus}\
\textit{University of Chicago}
There is enormous public interest in the successful use of endocrine therapy for the treatment of cancer. Newspapers and magazines daily extol the virtues of one product versus another. Tamoxifen is a household name and millions of people are now taking hormone antagonists in one form or another. This is the reason for writing this book.

We have lived through a revolution of translational research that, we believe, can be used as a model for future progress. The principle was simple—find a target in the cancer cell and attack a critical pathway for growth. But at the start, there was no guarantee of success. History is lived forward, but written in retrospect. We know the end before we describe the beginning and so we can never really recapture what it was like.

Thirty years ago, when we were starting our careers in endocrinology and pharmacology, the treatment of breast and prostate cancer was very different from what it is today. Patients were treated in the later stages of the disease based on clinical observations and experience accumulated over three generations. Strategies were not mechanism-based, although translational research had been important in defining the role of the ovaries and the testes in the growth of breast and prostate cancer, respectively.

In the case of breast cancer, radical mastectomy was the standard of care, with radiation therapy available to control recurrences. Advanced breast cancer was showing encouraging responses to combination chemotherapy, which led to the widespread belief among the medical community (that is still held by many today) that the appropriate cocktail of new and powerful chemotherapies would be found that would cure cancer. Adjuvant chemotherapy was not an option because the concept of destroying the last micrometastasis after “curative” surgery had not yet evolved into the lexicon of clinical trials. Although hormonal therapy had fewer side effects than any of the chemotherapies, the clinical studies in the 1950s and 1960s had proven, to the satisfaction of nearly everyone, that endocrine therapy was not a useful path for clinical investigation. High dose estrogen or androgen therapy showed advantages for about a year in one third of postmenopausal women with metastatic disease. Diethylstilbestrol produced higher response rates in prostate cancer, but most patients relapsed and many had serious cardiovascular complications caused by the therapy. The medical and scientific community concluded that hormonal approaches could not provide
any long-term benefits for patients. Rather than adding high doses of hormones, the other strategy was endocrine ablation to remove the ovaries, adrenal glands, or the pituitary gland. These approaches could be life-threatening and, more often than not, did not produce any beneficial response for the patient. Clearly, a test was needed to predict who to treat successfully, thereby avoiding unnecessary surgery.

The treatment of prostate cancer was also empiric. Although Professor Charles Huggins had received the Nobel Prize in 1966 for his contributions to the endocrine control of prostate cancer, it is fair to say that basic research on prostate cancer was at least a decade behind breast cancer research at this time. Nevertheless, the seeds for success had been sown that would develop into a molecular approach to drug treatment in the 1970s.

Elwood Jensen synthesized the first high specific activity tritiated estradiol and showed that it was localized and retained in the estrogen target tissues of immature rats. Jensen proposed the existence of an estrogen receptor (ER) that modulated estrogen action within different target cells. He thus established the molecular foundation for steroid endocrinology. But perhaps of greater importance, he also translated this knowledge to propose that the ER assay would predict the response of breast cancer patients to endocrine ablation. However, the concept that the presence of ER would predict endocrine responsiveness only became widely accepted following an NCI conference in Bethesda in 1974. Jensen had solved the important issue of targeting ablative therapy to those who were most likely to respond but perhaps more important, in our view, he identified a target for rational drug discovery. Unfortunately, in 1970, there was little or no enthusiasm for drug development in this area.

The first nonsteroidal antiestrogen was discovered serendipitously in the 1950s by Leonard Lerner and associates at the William S. Merrill Company, Cincinnati, but the analogs were not developed for cancer therapy because of toxicological concerns. One compound, clomiphene, was developed to induce ovulation in subfertile women, but the original enthusiasm that nonsteroidal antiestrogens would be effective “morning after” contraceptives had waned by the late 1960s. No one was suggesting research in antiestrogens as the way to a successful career. However, Arthur Walpole and Dora Richardson working at the laboratories of ICI Pharmaceuticals (now AstraZeneca) in Alderley Park, Cheshire, discovered a novel series of triphenylethylenes with reduced toxicity. In the patents, it was recognized that the drugs had the potential to regulate the reproductive cycle and to treat hormone-dependent cancers. The latter application alone, if it were achieved, would be a major advance as there
would now be little need for ablative surgery. Walpole was the head of the Fertility Control Program at ICI Pharmaceuticals throughout the 1960s and his work provided the basis for the development of tamoxifen for the induction of ovulation and for the treatment of advanced breast cancer in the 1970s. Unfortunately, Walpole died in July 1977 and never saw the full application of the results of his discoveries. He was an outstanding individual who was responsible not only for antiestrogens but also for the investigation of drugs that regulated gonadotrophin release. His contributions were essential to the progress we see today in the endocrine treatment of both breast and prostate cancer.

Nobel Laureate Dr. Charles Huggins, founding Director of the Ben May Laboratory for Cancer Research (left), and Dr. Elwood Jensen, his successor (right).

We are, therefore, both beneficiaries of Walpole’s legacy. Walpole played an important role in our careers by encouraging us to develop our own ideas. One of us (VCJ) experienced Walpole “the PhD thesis examiner” in 1972 for a study of the structure activity relationships of nonsteroidal antiestrogens at Leeds University. Walpole subsequently approved the resources to conduct the first laboratory studies of tamoxifen (then ICI 46,474) as a treatment and preventative for breast cancer in laboratory animals. These studies by VCJ were conducted at the Worcester Foundation between 1972 and 1974 so the results could
be used to support clinical trials in the United States. Also, with the help of Elwood Jensen, then Director of the Ben May Laboratories at the University of Chicago, studies showed that tamoxifen blocked estradiol binding to human ER. Walpole subsequently strongly supported a Joint Research Scheme between Leeds University (VCJ) and ICI Pharmaceuticals (1975–1979). The results of this collaboration identified the potential of antiestrogens with high affinity for ER and the relationship between duration of tamoxifen treatment and the effectiveness of the antitumor actions. This was a key discovery for the future clinical application of tamoxifen as an adjuvant therapy.

One of us (BJAF) was recruited to ICI Pharmaceuticals in 1972 by Arthur Walpole to work in the Reproductive Endocrinology Group. His leadership and encouragement led to the discovery, with Dr. Anand Dutta, of the LHRH agonist, Zoladex, and its depot formulation with Dr. Frank Hutchinson. Although Walpole also supported strongly the antiandrogen project that led to the discovery of what is currently the leading antiandrogen, Casodex, sadly he did not live to see this triumph either.

Today, tamoxifen has reached its full potential as an endocrine agent used to treat all stages of breast cancer. Millions of women with breast cancer have benefited from the use of tamoxifen. Long-term adjuvant tamoxifen therapy is proven to save lives, and it can be estimated that 400,000 women are alive today because of this appropriate treatment strategy. The recognition that tamoxifen was becoming a “treatment of choice” encouraged the subsequent development of selective aromatase inhibitors and pure antiestrogens and pioneered the development of a whole new drug class: the selective estrogen receptor modulators (SERMs) to treat osteoporosis and to test in the prevention of coronary heart disease and breast cancer.

The lessons learned with tamoxifen were applied to prostate cancer with the development of nonsteroidal antiandrogens and luteinizing hormone releasing hormone (LHRH) superagonists to interrupt gonadotrophin release. These latter agents are used to treat both breast and prostate cancer.

The chapters in *Hormone Therapy in Breast and Prostate Cancer* describe the laboratory and clinical development of concepts that are now successfully applied for the treatment of breast and prostate cancer. We are pleased to thank our friends and colleagues who have contributed to the chapters and created a balance of history, laboratory discovery, and clinical practice. Our book is offered as a foundation and guide to progress for researchers and clinicians alike.
The clinical progress during the past three decades would not have happened but for the conceptual shift in reasoning that occurred in the early 1970s. The central role of steroid receptors in our story was the direct result of Elwood Jensen’s seminal studies in translational research. We are honored that Professor Jensen generously agreed to write the Foreword for our book.

V. Craig Jordan
Barrington J.A. Furr
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1. INTRODUCTION

The reduction of circulating steroid hormones or the blockade of steroid action in cancer tissue are primary goals in the current strategy of breast- and prostate-cancer treatment. Antiestrogens, antiandrogens, aromatase inhibitors, and highly potent luteinizing hormone-releasing hormone (LH-RH) agonists (used to desensitize the pituitary gland and perform a “medical hypophysectomy”) are all drugs that have been proven to be valuable cancer treatments over the past two decades. However, the knowledge that there is a link between sex steroids and growth of some breast and prostate tumors has taken a century to piece together.

In 1896, George Beatson (1) reported that some premenopausal women with inoperable advanced breast cancer could benefit from the removal of the ovaries. Beatson based his strategy on the knowledge that the histology of mammary tissue could be affected in rabbits or farm animals by spaying. One could argue that these data, from a single physician, were the first successful attempt to conduct translational research in breast cancer. In a similar vein, Stanley Boyd at the Charing Cross Hospital could be said to have performed the first “clinical trials overview” of the effect of oophorectomy to treat advanced breast cancer in premenopausal women. Boyd collected information on 54
patients who had undergone oophorectomy and found that about 30% had an objective response to the procedure (2). This important result has defined the response rate of advanced breast cancer to any good single agent endocrine therapy since that time. The identification of individual tumors that were more likely to respond to endocrine therapy did not become a clinical reality until the 1970s. In the late 1950s, Jensen discovered the estrogen receptor (ER) (3) and proposed a predictive test for hormone-responsive breast cancer based on the identification of ER in tumors (4) (Fig. 1). However, if the receptor is the target for antihormonal therapy, the evolving understanding of hormone synthesis and action has also played a pivotal role in current treatment.

The discovery of an estrogenic principle in the follicular fluid of pig ovaries by Allen and Doisy in 1923 (5) was a major breakthrough that proved to be invaluable in all future research endeavors in the area. Allen and Doisy established a vaginal-cornification assay in ovariectomized mice to identify estrogenic compounds (5) and Doisy subsequently crystallized the first steroid hormone estrone in 1929 (6).

Historically, the vaginal cornification assay was important to identify synthetic estrogens during the 1930s (7–9) and was used to demonstrate the potency of the synthetic nonsteroidal estrogen diethylstilbestrol (DES) by Sir Charles Dodds (10). High doses of DES were subsequently used for the successful treatment of

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Fig. 1. Estrogen-target tissues around a women’s body. The appreciation of the regulation of menstrual cycle and the mechanism of estrogen action has been key to the use of nonsteroidal antiestrogens in the treatment and prevention of breast cancer.
both prostate (11) and breast cancer (12). This work was pioneering because the reported success of pharmacological doses of a synthetic estrogen heralded the era of chemotherapy for cancer. The mechanism of action of DES in suppressing growth of prostate cancer was clear: it prevented secretion of luteinizing hormone from the pituitary gland, which consequently led to a fall in androgen secretion from the testes. In essence, this produced the first medical castration. Although the actual mechanism of action of high-dose estrogen is obscure in the case of breast-cancer treatment, the therapeutic approach proposed by Professor Paul Erhlich at the turn of the century that a drug could be synthesized to produce selective toxicity on bacteria (13), now became a reality for cancer. However, a full understanding of steroidogenesis and the control of the reproductive system was necessary before a logical strategy of targeted drug development could be fully implemented.

The discovery that the pulsatile release of a small peptide, known as LH-RH, regulates the secretion of luteinizing and follicle-stimulating hormones (FSH) was initially viewed therapeutically as a way to induce ovulation in infertile women and stimulate spermatogenesis and androgen production in infertile men (14). However, the finding that the pituitary gland becomes rapidly desensitized by prolonged stimulation with LH-RH raised the possibility that contraceptive agents could be developed (14). Sustained release preparations of highly potent LH-RH agonist analogs effectively produce a medical oophorectomy and stop ovarian-estrogen synthesis in women and testicular-androgen synthesis in men (15). The application of sustained release preparations used to treat premenopausal breast cancer and prostate cancer is now known to be an effective therapy, thereby avoiding surgical procedures and endocrine ablation (16,17).

Breast-cancer incidence increases with age, but the same proportion of postmenopausal women respond to endocrine therapy as premenopausal women. The ovaries are the primary site for estrogen synthesis but significant levels of estrogen are produced by postmenopausal women. The adrenal glands are an important site for steroidogenesis. Huggins and Bergenstal (18) found that adrenalectomy, with maintenance of patients on cortisone acetate, could cause some regression of late advanced breast and prostate cancer. Hypophysectomy (19,20) was also effective but morbidity was high and patients again had to be maintained on corticoids. In fact, high doses of corticoids alone were also able to control adrenal steroidogenesis. However, the finding that the steroid androstenedione was converted to estrone (21,22) in postmenopausal women and that there was significant local production of estrogens by aromatization in breast cancers (23,24), provided a rationale to explain the efficacy of inhibitors of aromatization as therapeutic agents in breast cancer (25–27).

If estrogen and androgen are essential to cause the growth of breast and prostate cancer, then antagonist drugs that block hormone action would be
valuable therapeutic agents. The discovery of antiestrogens built on the extensive knowledge that nonsteroidal estrogens could be identified rationally (7–9). Lerner and coworkers (28) reported the first nonsteroidal antiestrogen, MER25 in 1958. This simple triphenylethanol had only antiestrogenic actions and no other hormonal or antihormonal properties. However, MER25 was too toxic for clinical use and analogues of the estrogen triphenylethylene were investigated. Harper and Walpole (29) reported that ICI 46,474 (tamoxifen) was a potent antiestrogen in the rat and this was pursued as a treatment for advanced breast cancer (30). Today, tamoxifen is the endocrine treatment of choice for all stages of breast cancer and the first drug to be approved (in the United States) for the reduction of the incidence of breast cancer in high-risk women (31,32).

The world-wide success of tamoxifen encouraged a close examination of the mechanism of action. The discovery of the ER by Jensen (3) and the proposal to use the ER assay to identify women who were more likely to respond to a hormonal treatment played a fundamental conceptual role in the use of tamoxifen to treat breast cancer. It is now known that tamoxifen is more likely to enhance the survival of women with ER-positive tumors (31) and prevents the development of ER-positive breast cancer (32). However, the discovery of selective ER modulation with tamoxifen and keoxifene (now called raloxifene) in the laboratory (33,34) and the demonstration that tamoxifen and raloxifene have estrogen-like effects on bone (35) but antiestrogenic effect on the breast has opened the door to new opportunities for the discovery of novel compounds to treat a number of diseases associated with the menopause such as osteoporosis, coronary heart disease, and breast and endometrial cancers (34–37).

New knowledge about estrogen action has been advanced by the sequencing and cloning of the ER (38–39) and the discovery of a new ER (40) that modulates estrogen action in different tissues around the body of both males and females. The classical ER is referred to as ERα and the new receptor is ERβ (Fig. 2). What is particularly interesting is the fact that ERβ was discovered by examining a cDNA library from rat prostate and that it appears to act antagonistically to the classical ERα. The tools of molecular biology have demonstrated that the endocrinology of the different sexes can be interrelated at the subcellular level.

Considerable effort is now focused on attempts to improve further response rates and duration of remission in breast cancer by other endocrine manoeuvres. Depot administration of the LH-RH agonist, Zoladex, was shown to be as effective as combination cytotoxic chemotherapy in premenopausal women with ER-positive breast cancer and was much better tolerated in the ZEBRA trial (41,42). Combination of LH-RH agonists with tamoxifen gives greater efficacy in pre-peri-menopausal breast-cancer patients than either agent alone (43–45).

The newer aromatase inhibitors have been shown to be at least equivalent to tamoxifen, the gold standard in postmenopausal women with advanced
breast cancer (46) and trials are now in progress to delineate their role in adjuvant therapy. Building on the observations made by Harris and colleagues (47) over a decade ago, that epidermal growth factor (EGF) receptor content of breast tumors was inversely correlated with ER and response to contemporary endocrine therapy was poorest in tumors with high EGF content, new trials are evaluating EGF receptor tyrosine kinase inhibitors as endocrine therapy in breast cancer: promising preliminary results have been reported (48). Thus, it seems likely that we are again on the threshold of significant improvements in therapy for breast cancer but careful and logical clinical trials supported by strong preclinical studies are necessary to realise this exciting potential.
Preclinical and clinical research in prostate cancer reflects the advances made in breast cancer, although progress has lagged behind until recently. Professor Charles Huggins, the Nobel Laureate, was the first to reason that castration would improve the prognosis of prostate cancer by androgen withdrawal (11). Antiandrogens that block the binding of dihydrotestosterone to the androgen receptor (AR) in the prostate, and thereby prevent androgen stimulation of prostate-cancer growth have now been discovered and developed clinically.

Cyproterone acetate was the first clinically effective antiandrogen produced by Neumann and colleagues at Schering AG (49). It proved effective in prostate cancer, but had a range of steroid-related side effects including liver toxicity. It was also a potent progestin and suppressed libido. The subsequent discovery of a nonsteroidal antiandrogen, flutamide by Neri and associates at Schering-Plough (50) was a major step forward because this was a pure antiandrogen that had negligible effects on libido: it still had some hepatotoxicity and caused diarrhea in some patients, but due to its short half-life had to be given three times a day. The discovery and development of the pure nonsteroidal antiandrogens, nilutamide (51) and Casodex (52), allowed once-daily dosing to be introduced. Casodex has now become established as the antiandrogen of choice based on its proven efficacy and its superior tolerance and half-life. Casodex (150 mg) monotherapy is as effective as castration in Mo prostate-cancer patients but without the psychological morbidity (53). Recent results show that Casodex monotherapy is also effective in men with early prostate cancer (54). This is consistent with preclinical data showing that early endocrine intervention is superior to delayed treatment (55) and with the results of an Medical Research Council clinical trial where castration given early was better than delayed treatment (56).

Combination therapy of LH-RH agonists with pure antiandrogens was heralded as a major breakthrough in improving response in patients with prostate cancer (57). Extensive trials with a range of LH-RH agonists and antiandrogens have given variable results and a single large trial of surgical castration alone vs combination with antiandrogen (58) failed to show any difference between the treatment arms. Meta-analysis of a majority of the trial data (59) has shown a small but significant advantage for combination therapy. It is possible also that there is a greater benefit for some subgroups than others. In the overview of these trials, it certainly appeared that pure nonsteroidal antiandrogens were more likely to be beneficial than cyproterone acetate.

Potent inhibitors of a 5α-reductase, like finasteride, have been shown to reduce markedly production of the potent androgen, 5α-dihydrotestosterone, but this is accompanied by increased concentrations of testosterone (60). Since testosterone can also bind to the androgen receptor and effect cellular proliferation, this may explain why results with finasteride in treatment of prostate cancer have been disappointing (61).

Just as with breast cancer, there are several new endocrine approaches being evaluated in prostate cancer. LH-RH antagonists (62) are being used and
appear to give comparable results to surgical castration and LH-RH agonists. Claims that they have longer-term clinical advantages, particularly as a result of lack of a transient initial rise in testosterone frequently seen with LH-RH agonists, have yet to be substantiated in randomized clinical trials. LH-RH antagonists appear to have an acceptable safety profile and histamine-releasing effects have been eliminated in the newer agents, but clinical experience, at present, is far more limited than with LH-RH agonists.

EGF receptors have also been found in prostate cancer (63) and EGF has been shown to induce cellular proliferation (64). Potent inhibitors of EGF receptor tyrosine kinase have, therefore, also been used to inhibit prostate-cancer growth in early clinical trials (65).

The pace of research in prostate cancer is accelerating and we can expect significant further advances in the next few years, both in new treatment options and effective therapies in early disease and premalignant conditions such as prostate intraepithelial neoplasia.

2. STRATEGIES FOR THE ENDOCRINE TREATMENT OF CANCER

This volume describes the enormous advances that have been made in the treatment of breast and prostate cancer by the rational application of endocrine pharmacology. Thirty years ago, novel endocrine therapy for breast and prostate cancer was not viewed clinically as a priority for investigation. This perspective has changed and hundreds of thousands of patients are alive today because of improvements in endocrine therapy. The story traces the collaboration between the laboratory and clinic to provide safe and effective medicines to aid patients with cancer. Indeed, the effectiveness of endocrine therapy has resulted in the testing of the worth of tamoxifen as a chemopreventive in well women (32) and its approval as the first preventive for any form of cancer.

The description of the target site specificity of steroid hormones and the regulation of steroidogenesis through the hypothalamic-pituitary axis have been fundamental to the current strategies that can rationally regulate the flow of steroids to a tumor site.

We believe it is appropriate to summarize the principal therapeutic strategies that have proved, through clinical trials, to be successful approaches to control tumor growth.

Most of the work was originally focused on postmenopausal patients with metastatic breast cancer (Fig. 3). Antiestrogens bind specifically to the ER in the breast tumor so the action of the group was a direct application of the emerging knowledge of estrogen actions in its target tissue during the 1960s (3). In contrast, aminogluthethimide restricted the availability of circulating estrogen in postmenopausal women. Aminogluthethimide blocks the biosynthesis of steroids in
Fig. 3. The evolution of strategies for endocrine treatment of advanced breast cancer in postmenopausal patients. Antiestrogens block estrogen action in the tumor. Amino-glutethimide blocks steroidogenesis in the adrenal glands and the conversion of androstenedione by aromatase enzymes in peripheral body fat. Aromatase inhibitors are available that block the enzyme specifically.

Fig. 4. Premenopausal women with advanced breast cancer can be successfully treated with either LH-RH agonists (that cause a chemical oophorectomy by blocking gonadotrophin release) or tamoxifen a nonsteroidal antiestrogen. The combination is proving to be a valuable new treatment strategy.
the adrenal glands and blocks the conversion of androstendione to estrone by aromatase enzymes in the peripheral body fat. Although the approach of using aminogluthethimide was clinically successful, the incidence of side effects focused efforts on designing more specific agents. The result is a variety of aromatase inhibitors that are specific for the enzyme at peripheral sites.

The antiestrogen tamoxifen has been proven to be effective in premenopausal patients (Fig. 4) despite increases in circulating estrogen (66,67) caused by interruption of the hypothalamic-pituitary axis feedback system. The sensitivity of the hypothalamic-pituitary axis to falling estrogen levels from the ovary causes a reflex rise in gonadotrophins. Aromatase inhibitors are not used in premenopausal women because the powerful action of gonadotrophins can reverse ovarian aromatase blockade. Another strategy, that is proving to be successful in pre- and peri-menopausal women, is the use of sustained release preparations of LH-RH to cause desensitization of the pituitary gland. As a result, the reduction in gonadotrophins causes a medical oophorectomy. A combination of a sustained release preparation of an LH-RH agonist and an antiestrogen will effectively decrease further the availability of estrogen to the tumor as will combination of LH-RH agonist and aromatase inhibitor.

Similar treatment strategies are used in men to control the growth of androgen responsive prostate cancer (Fig. 5). LH-RH agonists/antagonists reduce androgen availability by preventing gonadotrophin release from the pituitary
gland and nonsteroidal antiandrogens specifically block androgen action in the tumor by binding to the androgen receptor.

Overall, this volume describes the evolution of these treatment strategies. This is a rapidly evolving story so we have chosen to contribute an updated chapter at the end of the book.

REFERENCES


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