Chapter 11

Hormonal treatment of breast cancer

The breast is a tubulo-alveolar gland. The secretory units of the breast are the alveoli. These units are so responsive to hormone modulations that promote growth or regression of the breast tissue. It is well established that development and location of the normal breast are regulated by hormonal factors, and local cell-cell interactions. The endocrine steroids, peptides, and other molecules produced by the glandular tissue of the ovaries, pituitary, endocrine pancreas, thyroid, and adrenal cortex are the best defined of these factors.

On a more local levels of control, additional hormone-like substances are also synthesized by mammary tissue e.g. paracrine hormones, and juxtacrine factors. These juxtacrine growth factors are growth regulatory molecules that modulate adjacent cells by contracting their receptors. A third class of local factors is known as the autocrine or intracrine hormones. These are molecules that are synthesized by one cell and act back on the same cell type through surface or intracellular receptors.

A central organizing principle of endocrine hormone action in the breast has emerged. Systemic hormones regulate local production of growth factors. The actions of hormone-induced growth factors, and the complex interactions of the multiple cell surface signaling pathways with other hormone-induced gene products regulate both normal and abnormal glandular function and development (Fig. 13.1.).

The postpubertal breast may be mature, but it is inactive. A proliferative phase occurs during pregnancy. This is followed by a lactating phase after labor, and then regression takes place. An involutional or atrophic phase occurs after stopping lactation and when menopause occurs. Minor physical changes also occur in some women breasts before and during the menstrual cycle. All these changes and phases are controlled by a complex network of hormone and growth factor action.

Stage-by-stage action of these regulatory factors on mammary gland growth and development is illustrated in fig. 13.2.

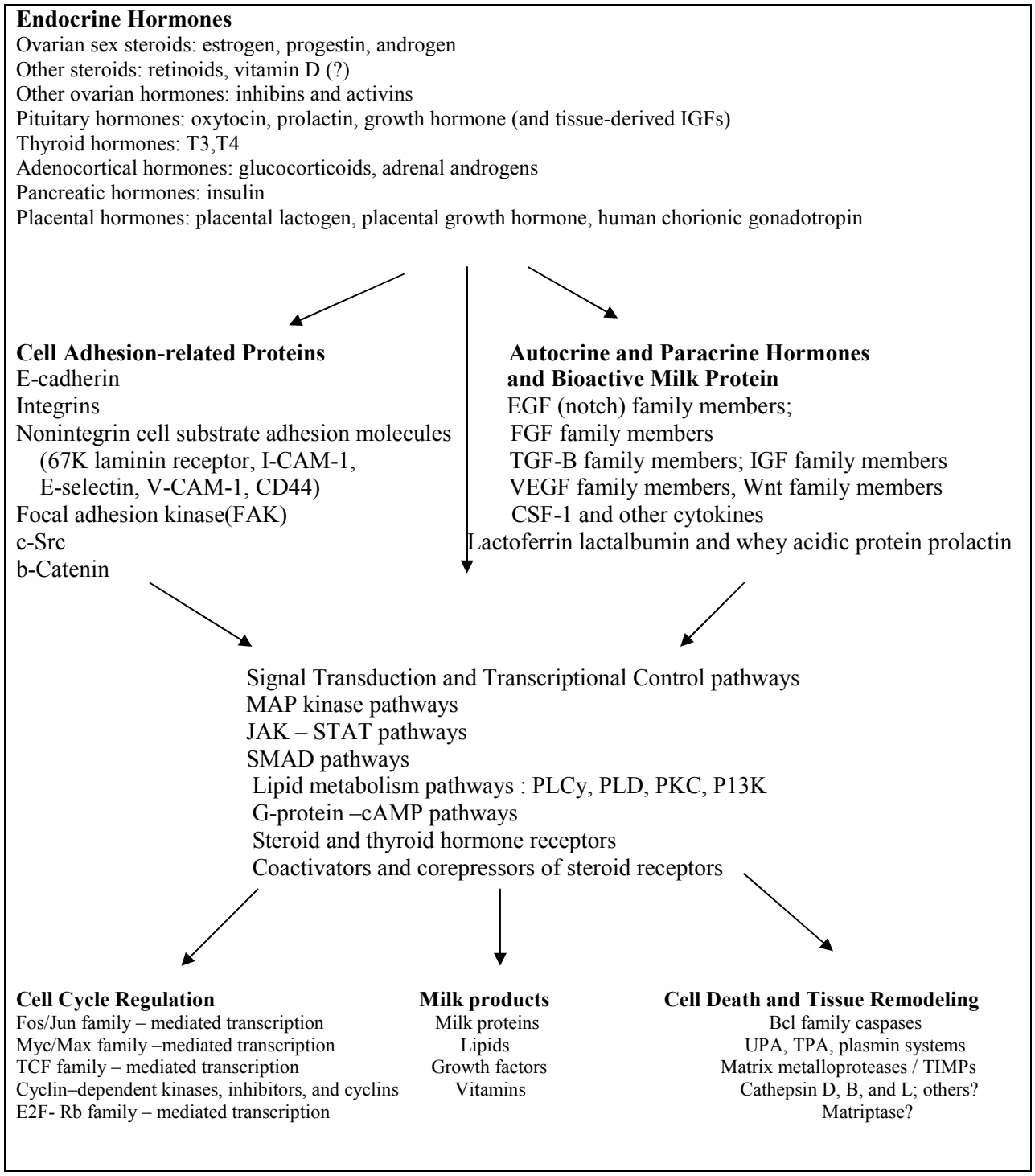

Figure 11.1 Hierarchy of modulators of breast development

cAMP, cyclic adenosine monophosphate; CSF, colony-stimulating factor; EGF, epidermal growth factor; FGF, fibroblast growth factor; GF, growth factor; IGF, insulinlike growth factor; JAK-STAT, Janus kinase-signal transducers and inactivators of transcription; MAP, mitogen-activated protein; P13K, phosphatidylionositol 3'-kinase; PKC, protein kinase C; PLC-γ, phospholipase Cγ, PLD, phospholipase D; TGF-β, transforming growth factor β; TIMP, tissue inhibitor metalloprotease; TPA, tissue plasminogen activator; UPA, urinary-type plasminogen activator; VEGF, vascular endothelial growth factor, Wnt, wingless

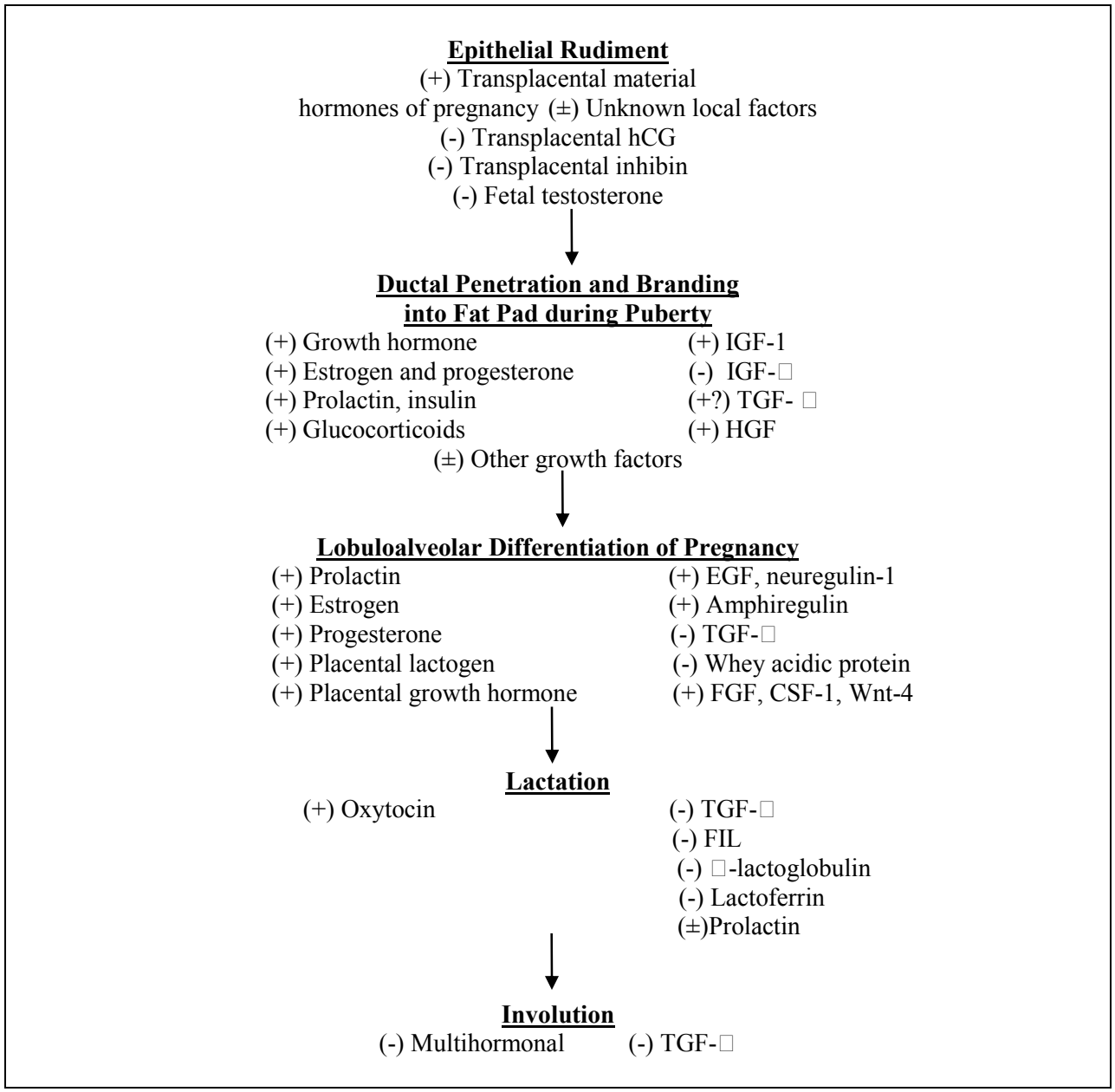

Figure 13.2. Stage-by-stage action of regulatory factors on mammary epithelium.

CSF, colony-stimulating factor; EGF, epidermal growth factor; FGF, fibroblast growth factor; FIL, feedback inhibitor of lactation; hCG, human chorionic gonadotropin; HGF, hepatocytes growth factor; IGF, insulinlike growth factor; TGF, transforming growth factor

HORMONAL THERAPY

An ovarian link that controls the growth of some breast cancers has been known for almost a century. The discovery of steroid receptors in the mid-1970s, however, has provided the rationale for a more selective application of endocrine treatment. Commonly, endocrine manipulations need a delay of 7 to 8 weeks before exerting their beneficial effects. So, all rapidly growing lesions are better treated with other forms of therapy.

I. Physiological and Biological Background

The hormonal environment of the breast is largely dependent on that part of the endocrine involving the hypothalamus, the pituitary gland and the ovaries (Fig. 13.3).

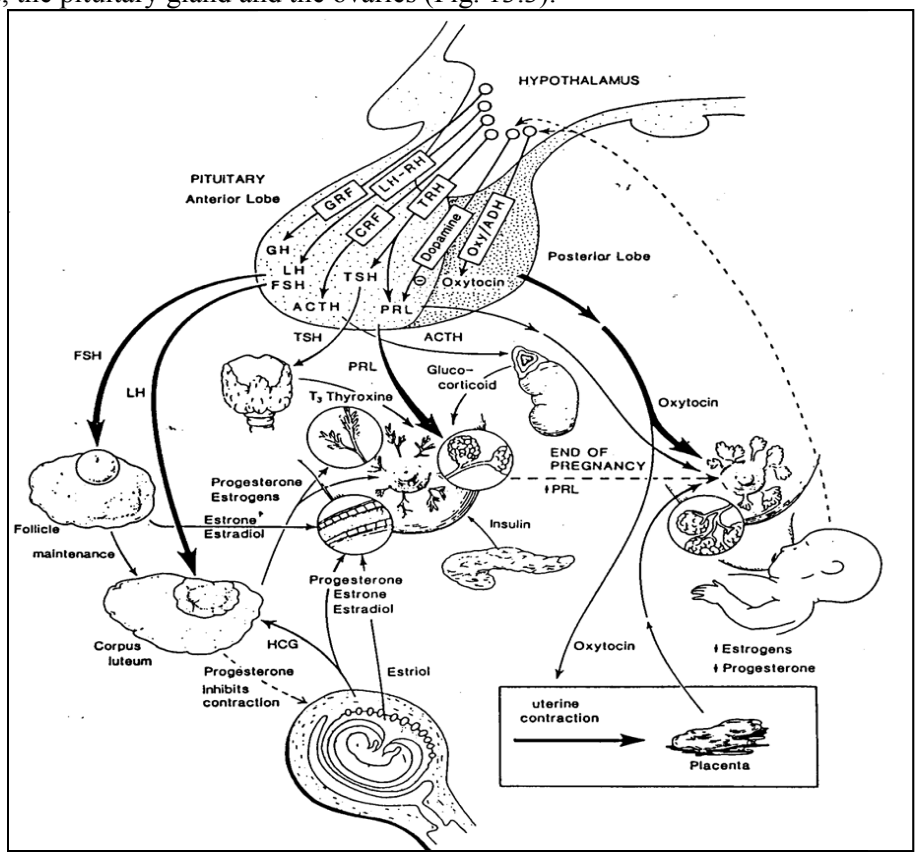

Figure 13.3.

Overview of the neuroendocrine control of breast development and function with relationship to gonadotropic hormones of the anterior pituitary and ovary.

Estrogen is the major stimulus for the growth of hormone-dependent breast cancer, and most forms of endocrine therapy are directed toward inhibiting, ablating, or interfering with estrogen activity.The ovary is the principal site of estrogen synthesis, but it is also synthesized by the adrenal gland, adipose tissue, and even by mammary tumors themselves.

After menopause, estrogens are essentially secreted by the adrenals. They are biosynthesized from cholesterol with a series of enzymatic steps including cleavage, hydroxylation, and aromatization. Ductal

growth is promoted by estrogen in the presence of growth hormone, while tubular development is promoted by prolactin and progesterone. The roles of cortisol, thyroxin, and insulin are permissive rather than regulatory.

Estrogens act by diffusing through the cell membrane to the interior of the cell, whether estrogens bind to ER in the cytoplasm or in the nucleus, the estrogen-ER complex then binds tightly to the hormone response element of target genes, and promotes the binding of a second complex to form a dimer.

When ER is activated by estrogen, the complex assumes a conformation that promotes specific gene transcription. Growth stimulation by estrogen is accompanied by an increase in growth stimulatory transforming growth factor alpha (TGFβ) production, whereas growth inhibition of hormone responsive breast cancer cell lines by an antiestrogen is paralleled by increased secretion of growth inhibition, TGFβ.

II. Hormone and Growth Factor Receptors

The genomic pathway of estrogen activation involves interaction of estrogen with a nuclear receptors protein that retains estrogen in target cell nuclei. The estrogen receptor (ER) α protein consists of 595 amino acids, and is, like the recently discovered 485-amino acids ERβ, a ligand regulated transcription factor. Both receptors, expressed in different amounts in different tissues, can be activated with different affinities by steroids and non-steroidal compounds. Both ER isoforms possess six (A-F) similar functional dominations, each responsible for different functions like hormone-binding, hormone response elements, transcription activation functions (AFs) and initiation of gene transcription (Fig. 13.4).

When activated by hormone binding, the ER undergoes transformation which enables it to bind specific DNA sequences, termed estrogen responsive elements found in the vicinity of target genes. Subsequently, recruitment of co-activators and general transcription factors results in the formation of an active transcriptional complex and enhancement of target gene transcription.

During recent years we have seen a paradigm shift in our understanding of estrogen action. This is mainly due to the discovery of the second ER, ERβ which is the encoded by a separate gene from that ERα. Many organs express both ER-subtypes, but different cell-types within each organ may express different ERs indicating that ERα and ERβ have distinct functions in some instances.

Figure 13.4 Schematic diagram of estrogen receptor α functional domains.

The ER contains 595 amino acids (aa) with the functional domains labeled A through F and a central DNA-binding domain (DBD) and hormone-binding domain (HBD). The regions important for dimerization (Dimer) and transactivation functions (AF-1, AF-2a, AF-2) are shown. Region A/B is

important for hormone-independent ER transcription; region C is the DBD; region D is the hinge domain; region E is the HBD responsible for hormone-dependent transcription; region F is important for modulation of ER activity

ERβ is expressed in partially different tissues from ERα, notably prostate, ovary, lung, kidney, gastrointestinal tract and especially colon, as well as in tissues where ER is also found, e.g. breast, central nervous system, testis. ER predominates in the uterus and liver. It has clearly been shown that the benefit from endocrine therapy is directly proportional to the amount of ER present in the tumor.

1. Hormone Receptor Analysis

The ER has recently originally been determined with cytosol measurements and more recently immunohistochemically (IHC) or with cytosol measurements. The advantages of the cytosol measurements via a ligand binding assay, include the generation of numerical results across the whole of the likely concentration range, good reproducibility, full technical and clinical validation, inclusion of measures of receptor functionality and existing quality assurance schemes. Disadvantages include a relative large amount of tissue required, the necessary care over handling, storage, assay and data processing, the labor intensive nature of the assay, and the lack of information about the nature of the tissue being homogenized. As improved anti-ER antibodies became available, IHC assay replaced the ligand binding assay (LBA). However, there were again advantages and disadvantages. Advantages of IHC include the fact that routine, fixed.

material could be used, archival material could be assayed retrospectively, only small quantities of tissue are needed, receptor content could be related to morphology and there was a measure of cellularity, internal positive control was often provided by the normal epithelial tissue in the section. The disadvantages included the subjectivity, the lack of quantitation, the absence of any indication of functionality of the receptor,. the lack of standardization of staining, the absence of an appropriate quality Quality assurance schemes are now existing. Several IHC scoring of receptor have been proposed (and the lack of clinical validation. An 8-point scoring system from 0-5 points according to the proportion of stained nuclei, score combining the intensity of staining and proportion of stained nuclei like Allred score…proportion of nuclei staining and 0-3 for the intensity of staining, with corresponding clinical recommendations according to the final score has been proposed by Harvey and colleagues. It was concluded by these authors that IHC was probably the more clinical useful score. In another study by Gordts and colleagues with 299 breast cancer cases IHC was used in a semi quantitative method and scored between 0 and 300 (the H-score). In this study concordant results between LBA and IHC were observed in 230 out of 299 cases (77%) while 69 patients had discordant results (kappa=0.537). Thus for both LBA and IHC assay, the use of a single cut-off should be avoided and activity quantified, or stratified into categories.

2. Definition of Cutoffs for Receptors Status

Like most biological phenomena, endocrine responsiveness is a continuous variable dependent on levels of ER and, to a lesser extent, PR. This consideration has been lost with the increasing use of the semi-quantitative IHC. Establishing a threshold or lower range in which the likelihood of response is very low or nil is still important, however. In the past, cutoff points as high as 20 fmol/mg of protein were used to define ER negativity, perhaps with the notion of giving patients with the remaining “ER+” tumors the highest probability of responding. Because evidence indicates that tumors with even a small amount of measurable protein, 3 to 10 fmol/mg, have response rates in the 20% to 30% range, classifying them as negative has two deleterious consequences. First, patients may be denied a trial of hormone therapy, from which they have a good chance of benefiting; second, such classification can lead to the clinically erroneous impression that a substantial number of patients with ER- tumors benefit from hormone therapy. To avoid these pitfalls, stringently low cut points should be adopted. For example, evidence suggests that setting a cutoff for ER negativity of 3 fmol or less of ER protein per milligram of cytosol

protein by ligand assay and 1% of positively stained cells by IHC analysis best separates patients who do not derive benefit from endocrine treatment from those who do. When stringently low cut points are adopted, special attention to quality control is crucial to avoid variability and false-positive results.

3. Factors Influencing the Level of Steroid Receptors

Numerous clinical and physiologic factors must be considered when assessing the significance of a steroid receptor level. These include race, sex, age, menopausal status, day of cycle for premenopausal women, pregnancy and lactation, organ site, tumor cellularity and histologic differentiation, and history of drug therapy.

Relative to histopathology, it may be generally concluded that the presence of both estrogen and progesterone receptors implies retention of the regulatory mechanisms operating in normal breast epithelium. Thus, a loss of receptor may be taken with other neoplastic features as a mean for identifying patients at increased risk of tumor recurrence,

Several studies have not found a correlation between steroid receptor status and either the size or location of the tumor in the breast, the axillary node status, or the clinical stage of the disease.

The endocrine status of the patient influences the incidence and the concentration of steroid receptors in breast tumors i.e. being lower in premenopausal women than in postmenopausal ones. Clearly, patient age influences the level of receptors, higher concentrations are exhibited by tumors from elderly patients.

In general, the levels of specific steroid receptors in specimens of metastatic breast cancer are similar to those observed in primary tumors. However few studies suggest that there may be a progressive loss of receptor levels as the disease progresses.

The influence of therapies using cytotoxic drugs or antihormones was also studied. Allegra et al. suggested that intervening hormone therapy selectively eliminates estrogen receptor containing cells, but chemotherapy apparently has no or little effect. Also, as it is known that among criteria used to select therapy for breast cancer patients is the site of metastases, no correlation was generally found between the presence of steroid receptors and the organ site of metastatic lesions

4. Clinical Significance

ER and PR can be used as both predictive and prognostic factors. A predictive factor indicates the likelihood of a response (or no response) to a particular treatment – in the cases of ER and PR, to hormone therapy.

A prognostic factor is indicative of the inherent biological aggressiveness of a tumor, reflecting the natural history of the disease after local therapy. An example is nodal status. Prognostic factors are therefore most accurately assessed in systemically untreated patients, although in reality, most studies of prognostic factors contain a mixture of treated and untreated patients. Prognostic and predictive factors are not mutually exclusive – a given factor can be both prognostic and predictive, as in the case of ER and PR.

It has been demonstrated conclusively that the presence of estrogen receptors provides a molecular basis for the distinction between tumors that are responsive to hormone manipulation and those that are not. Analysis of approximately 8000 breast cancer specimens over a 10-year period has indicated that 60% to 65% of primary lesions and 45% to 55% of metastatic tumors exhibit more than 10 fmol/mg cytosol protein binding of estrogen receptors. Also, 53% of estrogen receptor positive tumors were responsive to hormone therapy. Furthermore, when the collective results from the NIH Consensus Development

Conference (1990) were summarized, the spectrum of response ranged from less than 6% when estrogen receptor levels were below 10 fmol/mg to more than 80% objective remissions when tumors contained more than 200 fmol/mg cytosol protein.

The prognostic value of estrogen receptor analysis in primary lesions was supported by several studies. Most of these studies indicated clearly that estrogen receptor status is useful in predicting the course of the disease as patients with breast cancer containing free estrogen receptors exhibited longer disease free survival than those whose tumors did not contain estrogen receptors.

An overview of trials of women with early-stage breast cancer who were randomized to adjuvant tamoxifen therapy versus no adjuvant tamoxifen therapy provides the best data for examining the relationship of ER and PR status to benefit from adjuvant hormone therapy. This meta-analysis involved more than 37,000 women in 55 trials; in general, follow-up is at least 10 years. The results clearly and unequivocally demonstrate that women with ER+ tumor derive significant benefit from 5 years of tamoxifen treatment in terms of reduction in odds of recurrence and death, whereas those with ER- tumors do not.

The simultaneous determination of the progesterone with the estrogen receptors is reported to increase the accuracy of selecting the patients who are most likely to respond to hormone therapy.

The relationship between estrogen receptor exhibition and response to chemotherapy, is remains no more controversial. Some Several studies suggest exhibit that a correlation exists between lack of receptors and response to chemotherapy. Others have reached different conclusions with opposite results, and even some of these authors were unable to demonstrate any relationship between receptor status of the tumor and patients response to chemotherapy.

So, in conclusion, it is recommended that both estrogen and progestin receptors should be analyzed in all tumor specimens from patients with breast cancer. Laboratories should comply with criteria assigned by quality assurance programs. Receptor profiles may be useful and used as a predictive indicator of an endocrine-responsive tumor, and as a prognostic index of a patient's clinical course.

Therapeutic Modalities

In 1896, Beatson's historic observations on breast cancer regression after oophorectomy provide the first insight into the estrogen-dependent nature of breast cancer. Further surgical research followed for almost a century with considerable vigor. Initially, researchers focused on procedures that removed other endocrine organs besides the ovaries e.g. resection of adrenal glands and pituitary. Starting in 1960s, ablative surgery began to be replaced by pharmacologic approaches, and currently, most patients are managed with medical rather than surgical forms of endocrine therapy.

Breast cancer endocrine therapies that target sex hormone receptors may be recently classified as follows:

1. Tamoxifen and Selective Estrogen Receptor Modulators (SERMs)

Tamoxifen has been the preferred hormonal treatment for breast cancer for the last 30 years. The decline in breast cancer mortality in western countries is considered to be in part because of tamoxifen. It is a nonsteroidal triphenylethylene that was first synthesized in 1966, initially as an oral contraceptive but activity in metastatic breast cancer was first described in the early 1970s. The dazzling favorable experience with the drug in the metastatic setting led to its use as an adjuvant therapy. Initially, tamoxifen was believed to be an antiestrogen in breast tissue through competitive inhibition of estrogen, binding to ER. With increasing experience, clinicians observed effects on several other organs. So, it is associated

with the development of endometrial cancer and venous thrombosis as a result of its estrogenic effects on endometrium and the coagulation system. It is also associated with beneficial effects on bone mineral density and blood lipid profile through the same estrogenic effect on bone and the cardiovascular system. Furthermore, the mixed agonist/antagonist actions of tamoxifen explain several well-described clinical syndromes associated with treatment with the drug including tamoxifen-induced flare reactions, and tumor regression after withdrawal of tamoxifen therapy.

So, although tamoxifen is the well established therapy to consider in all stages of breast cancer, the above mentioned side effects have led researchers to investigate new agents that retain favorable estrogenic properties in specific tissues and display antiestrogen activity on the endometrium. Such research has generated the concept of selective estrogen receptor modulators (SERMs) that mediate either estrogen agonist or estrogen antagonist effect in different tissues.

Ideally these drugs are antiestrogenic in the breast and retain beneficial effects on bone mineralization and blood lipid profile but do not exhibit adverse estrogenic effects on the endometrium. So, drugs such as tamoxifen that exhibit a mixed agonist/antagonist profile has been designated as SERMs. In 1998, however, a new SERM "raloxifene" was approved in the USA for treatment of osteoporosis. An early evaluation of raloxifene activity in tamoxifen-resistant breast cancer was disappointing, and little further clinical research directed toward metastatic breast cancer has been performed. Consequently, it is difficult now to know where to place raloxifene in the treatment of breast cancer.

A third-generation SERM, currently designated SERM3 have recently entered clinical trials. Preliminary results from phase I studies have been reported, and it appears safe and well-tolerated. Results from phase II and phase III trials should be available soon. However, none of the new SERMs, including idoxifene, droloxifene, and toremifene (Farestone®), has been found to have activity in tamoxifen-refractory patients.

2. Pure Antiestrogens

Two steroidal antiestrogens have been developed that have pure antiestrogen activity in all tissues; ICI 164,384 and the more potent ICI 182,780 (Faslodex®). Faslodex is not orally bioavailable and must be given intramuscularly on monthly basis. An initial phase II clinical trial in metastatic breast cancer reported promising results in tamoxifen-refractory population with a response rate of 37%. Menopausal side effects did not appear to be increased by therapy. Two large prospective randomized trials are underway comparing Faslodex to anastrozole in tamoxifen-refractory patients, and to tamoxifen in patients who have never received tamoxifen or not received the drug for at least one year.

Another pure antiestrogen, EM800 is also under trial. It is orally active and structurally related to raloxifene.

3. Estrogen Deprivation Therapy for Premenopausal Women

In subsequent clinical experience throughout the twentieth century, it has been demonstrated that oophorectomy results in objective responses in ~30% of unselected premenopausal patients with metastatic disease.

In the 1980s, LHRH-As were introduced providing an alternative to oophorectomy. Acting on the pituitary LHRH-A treatment first stimulates FSH and LH secretion and then profoundly suppresses the pituitary-ovarian axis, with a fall in estrogen to menopausal levels. Results from prospective randomized

trials have demonstrated that response rates to LHRH-A are comparable to those observed with oophorectomy.

More recently, a meta-analysis of four trials addressing the value of LHRH-A and tamoxifen combination in premenopausal women suggests that this combination is more effective than single-agent LHRH-A with more response rates and a modest improvement in progression-free and overall survival.

The LHRH-A Goserelin has also been used as a component of adjuvant therapy in early breast cancer. It appears to provide added benefit to cytotoxic chemotherapy, and has the advantage over ovarian ablation of being given for a period of time with return to normal hormonal status by stopping the use of the agent. Moreover, in more recently randomized comparisons of adjuvant chemotherapy and adjuvant ovarian ablation using either radiation, surgery or an LHRH agonist, with or without tamoxifen, results have failed to show any advantage for chemotherapy. However, in 3 of these six trials, the chemotherapy (IV CMF) was clearly suboptimal. Firm conclusions about this important question await further follow up, more events in some of these trials, and a meta-analysis of all of the studies.

4. Estrogen Deprivation Therapy for Postmenopausal Women

The therapeutic benefits of reducing estrogen levels by ovarian ablation or LHRH-A therapy are restricted to patients with functioning ovaries. As ovarian function declines, the relative proportion of estrogens synthesized in extragonadal sites increases, and eventually nonovarian estrogen predominate in the circulation. Peripheral tissue depend on the aromatization of androgenic precursors of adrenal origin (testosterone and androstenedione) to generate estradiol and estrone. Aromatase, the enzyme responsible for this conversion, is present in adipose tissue, liver, muscle and brain. Aromatase activity has also been identified in the epithelial and stromal components of the breast. Therefore, local synthesis of estrogens may contribute to breast cancer growth in postmenopausal women.

Aromatase inhibitors have different mechanism of action than antiestrogens and have been used primarily in the postmenopausal population. The first aromatase inhibitor to become commercially available was aminoglutethimide. Aminoglutethimide has demonstrated activity in the metastatic breast cancer setting (response rates of 20% to 40%) when compared to established second-line therapy with megestrol acetate. It produces effects on glucocorticoid production and is now used infrequently in the clinical setting due to side effects.

The new generation steroidal (exemestane, formestane) and non-steroidal (anastrazole, letrazole) aromatase inhibitors (AIs) act on peripheral and tumor aromatase and do not suppress adrenal function like aminoglutethimide. The most frequent side effects is nausea, and the risk of thromboembolic events is substantially lower than tamoxifen. By irreversibly (exemestane, formestane) or reversibly (anastrazole, letrazole) inhibiting peripheral and tumor aromatase, these drugs effectively reduce levels of circulating estrogens, thereby removing a growth stimulus for hormone sensitive tumors.

The efficacy and safety of many of these agents is already established in the treatment of postmenopausal patients with metastatic hormone sensitive tumors. Anastrazole (Arimidex®), letrozole (Femara®) and exemestane (Aromasin®) thus far have shown the most promise. However, it is unknown at this time if any drug is superior to the others. Fadrozole is being less potent and less specific, and formestane is less convenient and equivalent to tamoxifen and megace.

Equivalence to tamoxifen in terms of response rate, and superiority in terms of time to disease progression have recently been demonstrated for anastrozole in the first line treatment of metastatic breast cancer in two combined randomized trials of identical design. However, follow up is relatively short. In another study comparing letrazole to tamoxifen as front line therapy in 907 patients, the drug was significantly superior to tamoxifen as measured by overall response rate, time to progression and time to

treatment failure. In the adjuvant setting, recent evidence from clinical trials including the ATAC trial indicate that improvement in disease-free survival does not translate into improved survival. Upfront use of aromatase inhibitors cpild be recommanded only in women who have contraindications to the use of tamoxifen.

So, given the tolerability and efficacy of these agents in the metastatic setting, they are likely to play an increasingly prominent role in adjuvant therapy. However, their routine use in the adjuvant setting cannot be recommended outside clinical trials.

The success of AIs therapy in postmenopausal women has raised the issue of whether this approach might be successful in premenopausal women. Unfortunately, inhibition of ovarian aromatase activity is associated with polycystic ovaries and androgens excess caused by activation of the pituitary-ovarian axis. Thus AI therapy is contraindicated in premenopausal women. However, consideration is being given to treating premenopausal women who have advanced breast cancer with combinations of LHRH analogues and AIs. However, until more information becomes available, premenopausal patients resistant to tamoxifen and LHRH-A should be treated with megestrol acetate. The alternate is to offer oophorectomy followed by an AI.

5. Endocrine Therapy Using Sex Steroids

Progestins

The semisynthetic progestins: medroxyprogesterone acetate and megestrol acetate are the two most active agents of this class of hormones available for treating breast cancer patients. The mechanism of action of the progestins is not well understood. However, in vitro studies suggest direct antiproliferative effects on human breast cancer cell lines. They may also exert direct antiestrogenic action by increasing the oxidative activity of 17 beta-hydroxy-steroid dehydrogenase, thereby facilitating the conversion of estradiol to esterone. Progestins may exert additional antiestrogenic effects by suppressing estrogen receptor levels. They also may cause estrogen deprivation indirectly through suppression of pituitary ACTH secretion, resulting in reduced production of adrenal androgen precursors.

The most frequently used dose of medroxy progesterone acetate is 1000 mg/d given orally or intramuscularly for the first month followed by 500 mg/d once or twice each week. The therapeutic dose of megestrol acetate in common use is 160 mg/day in divided oral doses.

General side effects of progestins include facies lunaris, increased sweating, fine tremors, leg cramps, weight gain, fluid retention, hypertension, skin rash, hypercalcemia, worsening of diabetes mellitus, and hypertrichosis.

Androgens

Androgens, including testosterone, fluoxymesterone, and the less virilizing testolactone, are associated with response rates in the range of 20%. Major side effects include virilization and jaundice. Androgens are rarely used to treat metastatic breast cancer. If considered, fluoxymesterone (Haltestin) 10 mg orally twice a day is as effective and nontoxic as any other.

6. Combination Endocrine Therapy Versus Sequential Single-agent Therapy

Tamoxifen has been used in combination with androgens, estrogens and progestins. The general conclusion from such studies is that the addition of these sex steroids adds toxicity to tamoxifen therapy without any clear gain in clinical outcomes e.g. time to disease progression and overall survival. So, combining sex steroids with tamoxifen is not recommended. On the other hand, combining antiestrogen and estrogen deprivation in premenopausal women continues to intrigue investigators. The modest improvement in response rate, progression-free survival, and overall survival associated with the

combination of LHRH-A plus tamoxifen versus LHRH-A alone contrast with studies in postmenopausal women in whom the combination of tamoxifen and estrogen deprivation with aminoglutethimide is no more active than tamoxifen alone. However, the potential of combining an aromatase inhibitor (anastrozole) and tamoxifen against using each agent alone in the adjuvant setting is now being examined in the ATAC trial. Currently, there are no data on the combination of an AI with tamoxifen in the metastatic setting. Therefore, tamoxifen and AIs should be used in sequence and not in combination until the efficacy and toxicity of the combination have been fully examined.

Guidelines for endocrinal therapy

I. Hormonal Treatment for Metastatic Breast Cancer

An overall therapeutics strategy for treating patients with metastatic breast cancer is based on many factors including age, disease-free interval, hormone receptor status, and extent of disease. For women with limited and non-life threatening disease, elderly, or have estrogen-receptors-positive tumors, hormonal therapy is the initial treatment of choice. The following algorithm describes the preferred sequence of current hormonal options (Fig. 13.5).

It is likely that this algorithm will become outdated in the future in view of the pending clinical trials that will mature in the coming few years (Table 13.1).

II. Adjuvant Endocrine Therapy For Early Breast Cancer

The role of tamoxifen and other endocrine therapies in the management of patients with early breast cancer are clearly emphasized and explained in the overview analysis of the EBCTCG, NIH consensus and St. Galen recommendations reviewed in other part of this book.

It is important to recognize that adjuvant endocrine manipulations which is mostly 5 years of tamoxifen should be given for anyone with a tumor that is estrogen or progesterone receptor-positive, and that patients with tumors lacking both will not benefit by endocrine therapy. Also, for patients with node negative cancers less than 1 cm in diameter regardless of histologic grade, or tumors 1 to 2 cm in diameter of low grade, evidence of a benefit exceeding the detriments of hormonal therapy is lacking.

Future thoughts and new role of endocrinal therapy

Classically, “endocrine therapy” for breast cancer has implied interference with the signal transduction pathway mediated by the estrogen receptor. Disruption of other signal transduction pathways has been recently tried with promise for toxic-benefit ratios that are better than classic endocrine therapies.

Retinoic acid and its derivatives interact with a family of receptors with similar structural motifs as those of estrogen and progesterone receptors. It was suggested that one of the retinoic acid receptor agonist (ATRA) might reverse tamoxifen resistance. A new class of retinoids, designated rexinoids (Targretin®) has been well tolerated in phase I trials and it is being examined in phase II trials both as a single agent and in combination with tamoxifen.

Because resistance to endocrine therapy in ER positive tumors may be associated with overexpression of erbB2, trials of the combination of antibody targeting erbB2 (Trastuzumab) with endocrine therapy are appealing.

Class of agent	**Agents in trial**
Non steroidal AI vs. Progestin	Femara vs. Megace
Steroidal AI vs. Progestin	Exemestane vs. Megace
Non steroidal AI vs. Same	Femara vs. Arimidex
Non steroidal AI vs. Tamoxifen	Femara vs. Tamoxifen Arimidex vs. Tamoxifen
Pure antiestrogen vs. non steroidal AI	Faslodex vs. Arimidex
Pure antiestrogen vs. Tamoxifen	Faslodex vs. Tamoxifen

Table 11.1. Ongoing Endocrine Therapy Trials

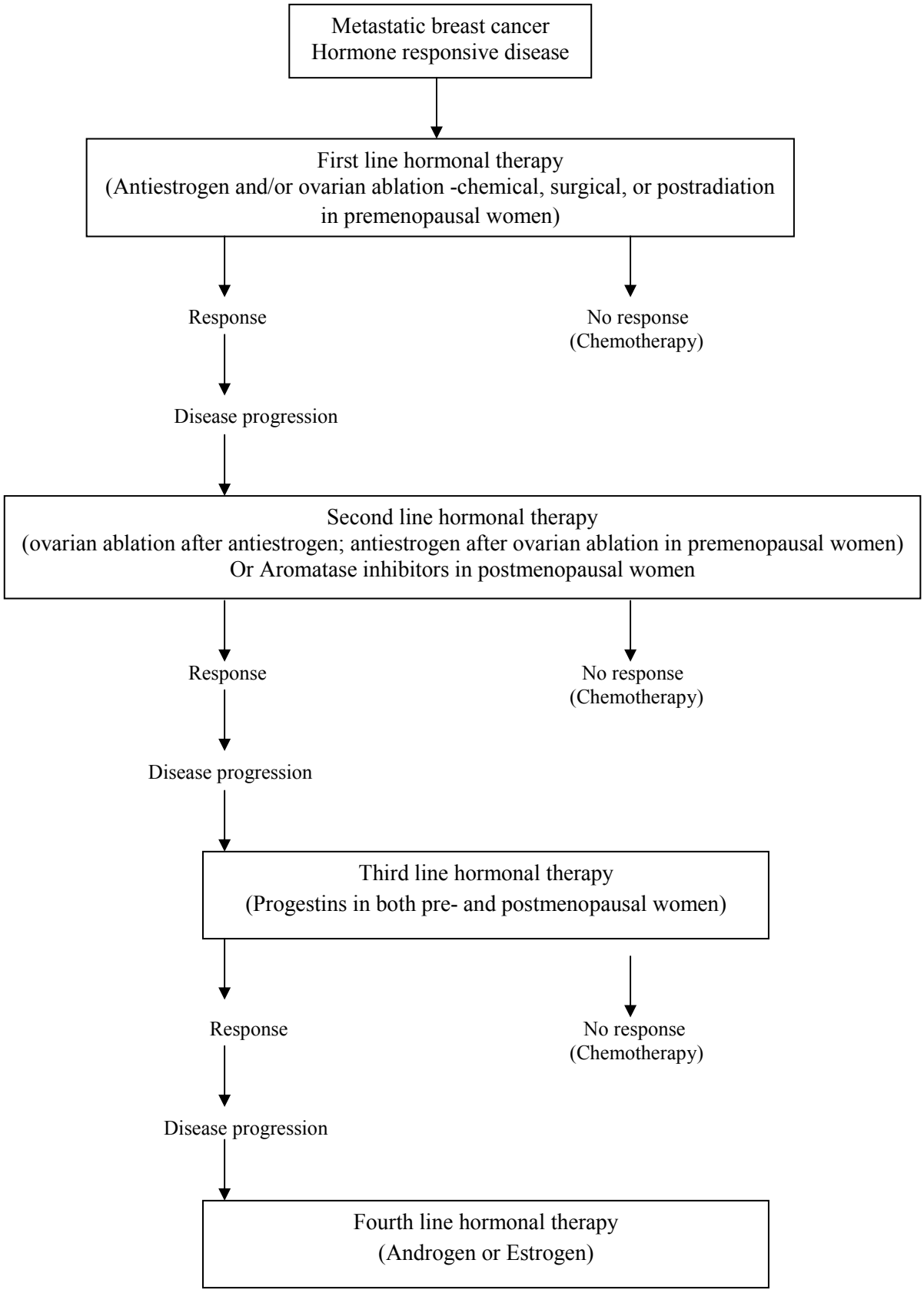
Metastatic breast cancer
Hormone responsive disease
First line hormonal therapy
(Antiestrogen and/or ovarian ablation -chemical, surgical, or postradiation in premenopausal women)
Response
No response
(Chemotherapy)
Disease progression
Second line hormonal therapy
(ovarian ablation after antiestrogen; antiestrogen after ovarian ablation in premenopausal women)
Or Aromatase inhibitors in postmenopausal women
Response
No response
(Chemotherapy)
Disease progression
Third line hormonal therapy
(Progestins in both pre- and postmenopausal women)
Response
No response
(Chemotherapy)
Disease progression
Fourth line hormonal therapy
(Androgen or Estrogen)

Figure 11.5.