ENDOCRINE TREATMENT OF BREAST CANCER
— A REVIEW

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Although complete cure is still not possible in advanced breast cancer, endocrine manipulation can lead to a longer overall survival in 30–40% patients. In comparison to cytotoxic therapy, compliance and quality of life is much better with endocrine treatment. It has an added advantage that if the disease becomes resistant to one group of drugs, it may still respond to another group of endocrine agents. As a general rule, only one agent is used at a time and the drug is changed only if the disease is advancing, not if it is static.

Introduction

Breast cancer remains the leading cause of death due to malignancy amongst women of reproductive age.1 In industrialized countries, 1 in 11 women will develop breast cancer.2 Patients with metastatic breast cancer are offered palliative treatment which may be in the form of local radiotherapy, chemotherapy, hormonal therapy or combination of these.3,4 It has been realized that even patients with advanced disease will respond to various treatment strategies.4 Endocrine or hormonal therapy is the first line therapy offered to patients with metastatic breast cancer, specially post-menopausal women. Response rate with endocrine therapies varies from 50-60%.5 Although none of these patients are cured, their quality of life and duration of remission remains better than for cytotoxic chemotherapy, which is generally accompanied by severe side effects.

The rationale behind the use of endocrine therapy in breast cancer is that human breast is known to be sensitive to hormones including estrogen, progesterone and prolactin. Therefore, it can be assumed that tumors arising in the breast tissue will also be sensitive to these hormones. This was first demonstrated by Beatson exactly 100 years ago, who showed that in a patient with breast cancer, ovariectomy resulted in regression of the tumour.6 Since these breast tumors responded to ovariectomy, adrenal-ectomy and hypophysectomy, they were termed as “hormone sensitive” tumors. As majority of these tumors depend on estro-gens, any reduction in the level of estrogens will result in tumor regression. Majority of these hormone sensitive tumors contain estrogen receptors (ER) in their cells. Patients with ER-positive tumors respond better to hormone therapy6 as is discussed later.

Clinical criteria for selection of patients for endocrine therapy:

Presence of the following factors are more likely to increase the chances of response to endocrine therapy:

a. Age (post-menopausal women)
b. ER-positive tumors

c. Tumors that have responded to hormone therapy previously

d. Slow growing tumors (long disease free interval)

e. Site of metastases (eg bone, soft-tissue metastases).9

The rate of response to endocrine therapy is slower than that of chemotherapy and may take 15 to 40 weeks to produce a partial response.10

**Estrogen synthesis and mechanism of action:**

Ovaries are the main source of estrogen in pre-menopausal women which converts intraovarian androgens to estrogens by the action of an enzyme, aromatize. This enzyme, in turn, is under the influence of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary. Some aromatize is also present in peripheral tissues and subcutaneous fat, which is the main source of estrogens in post-menopausal women. Thus the main source of estrogens in post-menopausal women is the adrenal glands and peripheral tissues (including the breast itself) where aromatization of androgen precursors takes place.11

Estrogen exerts its effect by binding to specific nuclear receptors known as ER.12 This binding leads to a conformational changes in ER which can now bind to the specific segment of DNA resulting in cell division.13 Thus, inhibiting the effect of estrogen will result in decreased cell division. This inhibition of estrogen action can be accomplished either by (i) reducing the supply of estrogen to the tumor, or (ii) by antagonizing the endogenous estrogenic stimuli with anti-estrogens (blocking of ER).

The supply of estrogen can be reduced by one of the following ways:

- Ovarian ablation
- Adrenalectomy
  (or medical adrenalectomy in the form of aromatize inhibitors)
- Hypophysectomy
  (or medical hypophysectomy in the form of gonadotrophin-releasing hormone (GnRH) analogues)

**HORMONAL MANIPULATION IN BREAST CANCER**

**A. Ovarian ablation:**

This can be done either by oophorectomy or by ovarian irradiation (1200–1600 rads in four days) in pre-menopausal patients.7,14 The overall response is approximately 30%15,16 with a mean duration of response of 16 months and mean survival of 30 months.17 Patients more likely to respond to ovarian ablation include pre-menopausal women with bone and soft tissue metastases or pleural effusion. Post-menopausal women (except 10%) fail to respond to this form of therapy.18 This mode of treatment has been mostly replace by medical forms of ovarian ablation (GnRH analogues).

**B. Adrenalectomy:**

Response rates following adrenalectomy range from 25–55%19 with an operative mortality of 1–4%.16 Mean duration of remission is from 1-2 years. This form of treatment is helpful in patients with bone metastases. It has now been replaced by “medical adrenalectomy” with aromatize inhibitors.

**C. Hypophysectomy:**

Response rates and duration of remission is the same as for adrenalectomy. This procedure is now replaced by GnRH analogues.

**D. Aromatize inhibitors:**

Aromatize is an enzyme that catalyze the conversion of androgens to estrogens.
Inhibition of this enzyme results in the suppression of estrogens to the level of adrenalectomy in post menopausal women. Newer, more specific agents have been developed which specifically blocks the production of estrogens and does not cause the unwanted effect of adrenal insufficiency.

a. Aminoglutethimide (AG): AG was developed as an anticonvulsant agent but was found to have a side-effect of causing adrenal insufficiency by inhibiting the synthesis of steroids.20 AG inhibits the earliest step in steroid synthesis (Conversion of cholesterol to pregnenolone) by inhibiting the aromatize enzyme which is necessary for the conversion of cholesterol to pregnenolone and then to androgens and estrogens. Thus AG results in the suppression of synthesis of estrogens from cholesterol in post-menopausal women.21,22 This also results in compensatory rise in ACTH thereby necessitating the administration of hydrocortisone in a dose of 40 mg/day. The usual daily dose of AG is 1 gm/day alongwith hydrocortisone 40 mg/day. Overall response rate is 30% with a median response duration of 12 months.21 It results in good control of the disease in the bone, soft-metastases respond poorly. Side-effects include lethargy, nausea, drowsiness and rash.

b. 4-Hydroxyandrostenedione (4-OHA): 4-OHA (formestane/Lentaron) is a potent "pure" inhibitor of the aromatize enzyme system. It specifically blocks the conversion of androstenedione to estrone and thereby to estradiol. It does not act at the early stages of conversion of cholesterol to pregnenolone and therefore does not cause adrenal insufficiency. It therefore has fewer side-effects compared to AG.19,26 Usual dose is 250 mg intra-muscular injection, fortnightly. Response rate varies between 25-40%.26,27 Studies have shown that post-menopausal women with advanced breast cancer have responded to Formestane irrespective of their previous response to other endocrine agents.27,28 Soft-tissue metastases generally show the best response to Formestane while visceral metastases show a poor response. Median duration of response is between 7-12 months. Adverse effects are minimal and include sterile abscesses at injection site, mild lethargy, leucopenia and facial swelling. Thus Formestane can be used as an effective second-line endocrine therapy in post-menopausal women with metastatic breast cancer.

c. Newer, third and fourth generation, non-steroidal, competitive aromatize inhibitors with greater selectivity and lesser toxicity have been developed. These include oral agents such as Fadrazole,23 Vorazole24 and the fourth generation inhibitor, CGS 20267 (Letrozole).25,26 These are sufficiently selective not to cause cortisol insufficiency. They lower estrogen levels by 50-80% and have a better anti-tumor effect.23,24 They have a minimal effect on aldosterone, testosterone, androstenedione and cortisol levels. Response rate varies between 30-35% and median duration of response is approximately 12 months.24

E. 3-B-Hydroxy-Steroid Dehydrogenase inhibitor (Trilostane):

Trilostane (Modrenal) is a synthetic compound that inhibits 3-B-Hydroxy-steroid dehydrogenase which converts pregnenolone to progesterone.29 Response rate is very low 15%. Many patients suffer from lethargy, nausea, serve diarrhea and dyspepsia. It is therefore not used as a single agent in the treatment of breast cancer. Since Trilostane is an adrenal antagonist similar to AG, therefore, corticosteroid replacement therapy is needed. It is used in post-menopausal breast cancer patients. Recommended dose is 240 mg/day increasing gradually to 960 mg/day.

F. Progestins:

The exact mechanism of action of progestins in breast cancer is not known but
some proposed mechanisms include:

i. Down-regulation of ER (thereby desensitizing the tumor to estrogenic stimuli).

ii. It decreases the conversion of estrone to biologically active estradiol by decreasing the enzyme estradiol dehydrogenase.

iii. Its activity leads to decrease in pituitary release of gonadotrophins.

iv. It also has a direct effect through progesterone receptor (PR).

Various progestogenic agents include:

a. Medroxy progesterone acetate (MPA): it is one of the most commonly prescribed drugs for second-line therapy of advanced breast cancer. Various dose ranges are used but majority of patients respond to a high dose treatment (1 gm/day). Recent studies have shown that plasma MPA concentration rather than the administered dose is the main determining factor for toxicity and response to therapy. Response rate for this synthetic progestin ranges from 20-30%. Soft-tissue and bone metastases respond better to MPA compared to visceral metastases. It also has the added benefit of producing weight gain in patients. Some studies have shown high dose MPA to be superior to Tamoxifen as a first line endocrine therapy. Side effects include abscesses at injection. MPA causes respiratory depression in patients with low respiratory reserve and therefore can not be recommended in patients with a low respiratory reserve or in terminal patients.

b. Megestrol acetate (Megace): Mechanism of action, response rate and side-effects are similar to MPA. Dose is 160 mg/day. It is effective in post-menopausal women with bone metastases who no longer respond to Tamoxifen.

c. Danazol: It acts by binding to progesterone receptor (PR). It possesses an anti-progestogenic activity, inhibits the release of gonadotrophins from the pituitary and inhibits steroid synthesis. Its usual daily dose ranges from 300-600 mg. Response rate is 15-25%. Toxicity includes lethargy, peripheral edema and hot flushes. It dose not seem to be of any use as a first or second-line therapy used alone in breast cancer patients.

G. Gonadotrophins release hormone (GnRH) analogues:

These agents are widely used as endocrine treatment for pre-menopausal breast cancer patients. The effect of GnRH analogues is same as ovariectomy or hypophysectomy. Mechanism of action of GnRH cell surface receptors in the pituitary gland. GnRH is delivered to the pituitary from the hypothalamus in pulses. GnRH interacts with cell surface receptor which is internalized. When the next pulse of GnRH is released in 90 minutes, further receptor synthesis has occurred by then. This new pulse is therefore detected by the new receptors on the cell surface. In case of administration of GnRH agonists, there is a constant pulse production of GnRH due to supraphysiological release of gonadotrophins. Therefore, the receptors are constantly internalized and no pulses from the hypothalamus can be detected by the cells in the pituitary and no estrogen synthesis takes place in the ovary. Suppression of estrogen is normally attained in three weeks. Response rate is approximately 30-40% with a median duration of response of over 15 months. Best response is seen in pre-menopausal women with soft-tissue involvement. It is administered as a depot injection every four weeks. GnRH analogues are ineffective in post-menopausal women (response rate is less than 10%). Preparations available in market include Goserilin, Buserilin, Leuprolrelin and Nefarelin. Side-effects include an initial increase in bone pain (flare phenomenon, which subsides in 2-3 weeks), hot flushes,
decreased libido, urticaria and peripheral edema.

H. Anti-estrogens

Anti-estrogens are the most important recent advances in hormone treatment of advanced breast cancer. Tamoxifen is the most widely used anti-estrogen and due to its widespread use there are more than six million women years of experience with Tamoxifen. Its overall response rate in ER-positive breast cancer patients is 30-50%. This compound binds to ER and block all the sites on ER thereby inhibiting the effect of estradiol. It also has weak estrogenic effect. Thus Tamoxifen slows estrogen induced growth by a mixture of agonistic and antagonistic effects. It is only effective in about 10% of pre-menopausal women.8 Response according to sites of metastases include soft-tissue (35%), viscera (29%) and bone (25%). It is used in a dose of 20-40 mg/day. Side-effects include mild nausea and vomiting, thrombocytopenia, hot flushes, weight gain, hirsuitism and an inflammatory flare. In UK and USA, Tamoxifen is also being investigated for prevention of breast cancer in patients at high risk of developing the disease.45,46

Newer anti-estrogenic compounds include Toremifene, 3-hydroxytamoxifen (Droloxifene), 4-hydroxytamoxifen, ICI 164384 and ICI 182780.

Toremifene is a new anti-estrogenic compound which is a triphenylethylen derivative and has been developed to improve the therapeutic-to-toxic ratio of anti-estrogens.43 It binds to cytoplasmic ER with high affinity and exhibits both estrogenic and anti-estrogenic activity just like Tamoxifen.44 It causes 70% reduction in estrogen levels and can be considered as an alternative to Tamoxifen as a first line hormonal treatment for ER-positive advanced breast cancer. Response rates ranging from 50-68% have been reported using doses of 60 and 240 mg/day in ER-positive patients with advanced breast cancer.47,48 A recent study showed no benefit of 200 mg/day.47 Median duration of response is 17 months. Side-effects include hot flushes, vaginal bleeding or discharge, peripheral edema, vomiting, dizziness etc. Which are of the same intensity as with Tamoxifen.49 Interestingly, Toremifene, in contrast to Tamoxifen, does not produce any hepatoproliferative effect in rats and has a greater anti-proliferative effect in the anterior pituitary and the mammary gland.50

Droloxifene (3-hydroxytamoxifen) is another new anti-estrogenic compound with 10 to 64-fold higher affinity for ER compared to Tamoxifen.53 Its toxicity profile is the same as for Tamoxifen.

ICI 164384 (4-hydroxytamoxifen) is another new “pure” anti-estrogenic compound that exerts its anti-proliferative effect not only in ER-positive but also in ER-negative breast cancer cell lines.50 Thus it may have an alternate mechanism of action which is not ER mediated. ICI 164384 when used in combination with anti-progestins, onapristone, shows an even greater reduction levels in the serum.51

ICI 182780 is another potent, specific, anti-estrogenic compound. It has significantly higher anti-estrogenic activity which is 10-fold greater that of ICI 164384.52 Thus ICI 182780 is a potential new compound for the treatment of advanced breast cancer.

OTHER HORMONAL AGENTS USED LESS FREQUENTLY IN BREAST CANCER

a. Estrogens

Alexander Haddow first reported the regression of breast tumor in post-menopausal women after oral administration of estrogen.54 Since then, various trials have
shown a response rate of 30% in post-menopausal women. Soft-tissue and visceral metastases respond frequently to estrogens. Median survival is 27 months. Preparations available in the market include Stilbestrol (5-15 mg/day), Premarin (7.5–15 mg/day) and ethinylestradiol (0.3 mg/day). Side-effect include anorexia, nausea, vomiting, fluid retention and breakthrough vaginal bleeding in a few patients. Patients with bone metastases should not be treated with estrogens since hypercalcemia may result from the administration of estrogens in these patients which may be fatal. In approximately 10% of patients, the tumor growth can be activated by estrogens. This form of treatment has now been replaced by Tamoxifen and other endocrine drugs which carry less toxicity.

b. Androgens

Androgens can cause remission in 10-20% of post-menopausal patients with metastatic breast cancer. Medium duration of response is 20 months and response rate increases with age. Androgens causes significant pain relief from bone metastases. Bone marrow failure with leucoerythroblastic anemia often respond to androgen treatment. Hypercalcemia occurs in about 10% of patients. Major side-effects include virilization, acne and hirsutism. Agents commonly used include fluoxymesterone and nandrolone. The relatively low response rate together with unacceptable side-effects and the availability of Tamoxifen has made this form of treatment obsolete.

c. Vitamin D analogues

It has been shown that over 85% of breast tumor contain 1–25-dihydroxyvitamin D receptors. Unlike estrogens, vitamin D inhibits proliferation and promotes differentiation in various cell types which is due to the presence of vitamin D receptors. 1,25-Dihydroxyvitamin D3 has been shown to inhibit breast cancer cells both in vitro and in vivo. Experimental studies in rodents using 0.1 ug of synthetic analogue, 1α,25-dihydroxyvitamin D3, given three times a week produced significant regression in breast tumors. One of the serious side-effects of this compound is the development of hypercalcemia due to the stimulation of bone resorption. Newer analogues of Vitamin D have shown reduced calcemic activity. Recent studies have shown a beneficial additive effect of this compound when given along with Tamoxifen. The potential application of the compound in breast cancer is unknown yet.

REFERENCES


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