13. Endocrine therapy in metastatic breast cancer

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1. Introduction

Breast cancer is the most common cancer diagnosis and the second leading cancer-related cause of death in American women. In 1996, it is estimated that there will be 185,700 new diagnoses of and 44,560 deaths due to breast cancer [1]. At diagnosis, approximately 5% of women have metastatic disease. Unfortunately, treatment of advanced disease is currently only palliative.

Endocrine therapy generally is well tolerated and because of the favorable therapeutic index, it is the treatment of choice for women with advanced breast cancer. In fact, randomized trials show no adverse effect on survival for patients initially treated with endocrine therapy rather than chemotherapy, although initial rates of response to chemotherapy tend to be somewhat higher [2-4].

Hormonal manipulation is a very effective treatment for metastatic breast cancer. Responses are seen in approximately one third of unselected patients and in at least 50% of patients with estrogen receptor- (ER-) positive tumors [5]. Well-defined factors associated with greater likelihood of response to endocrine therapy include 1) ER and progesterone receptor (PR) positivity, 2) late premenopausal or postmenopausal status, 3) older age, 4) a long interval from diagnosis to first recurrence (disease-free interval), 5) disease limited to sites outside viscera, such as bone and soft tissue, and 6) previous response to endocrine therapy [4].

The standard, first-line endocrine agent is tamoxifen. Second-line therapy includes progestins and aromatase inhibitors that have similar response rates but more side effects than tamoxifen.

2. The biologic basis of endocrine therapy

In 1896, Beatson first described a patient in whom oophorectomy caused regression of skin metastases [6]. This was the first hormonal-change manipulation noted to affect breast cancer progression. Indeed, ovarian ablation results in an overall response rate of about 35% in premenopausal women with metastatic breast cancer [7]. Various treatments have since been devel-
oped to suppress gonadal and/or peripheral estrogen production or to antago-
nize the stimulative effects of estrogens on breast cancer cells [8,9].

In the 1940s and 1950s, other ablative therapies, including bilateral surgical
adrenalectomy and hypophysectomy, were developed. These treatments,
although effective, had significant morbidity and occasional mortality. More-
over, ‘medical’ forms of endocrine ablation were found that were as effective
as surgical ablation [10,11]. Randomized trials have confirmed similar re-
sponse rates for adrenalectomy and tamoxifen and aromatase inhibitors
[12,13]. Small randomized trials have been done comparing hypophysectomy
with tamoxifen and with aminoglutethimide (AG) [14,15]. All yielded similar
results. Less radical procedures to achieve hypophysectomy, such as the
transsphenoid approach or radioactive implants, carry less morbidity and
mortality but are still fraught with more complications than medical hormonal
manipulation.

Breast cancer cells have steroid receptors for estrogens, progestins, gluco-
corticoids, and androgens. Treatment of breast cancer in premenopausal
women traditionally has involved removal of the ovaries, the source of estro-
gen, and, in postmenopausal patients, administration of pharmacological
doses of estrogen. (In postmenopausal women, large doses of estrogen can
cause tumor regression.) The exact mechanism of these treatment modalities
and the effects of estrogens and antiestrogens on the breast cancer cell are not
fully defined. Our current understanding is that estrogen downregulates ERs,
decreasing the hormone’s effects [16].

Breast cancer cells also secrete other growth factors that are auto-
stimulatory (autocrine) and/or are stimulated by substances secreted by sur-
rounding cells (paracrine) (figure 1). Receptors for epidermal growth factor
(EGFR) and c-erbB2 (Her-2/neu) are found on breast cancer cells. EGF
and transforming growth factor alpha (TGF-alpha) interact with the EGFR
and activate tyrosine kinase, a signal transduction pathway shown to induce
proliferation of breast cancer cell lines in nude mice [17].

TGF-alpha can act as an autocrine or paracrine growth factor, and some
breast cancer cells produce TGF-alpha in response to estrogens. Receptors for
TGF-beta also are present on breast cancer cells (primarily those that are ER
negative). Using antibodies against TGF-alpha or EGFR to block TGF-
alpha’s effects can inhibit the growth of some breast cancer cells. Insulin-like
growth factor (IGF) also is produced by breast cancer cells in vitro and may
result in both autocrine and paracrine mitogenic effects [18]. Factors that
increase IGF production include estrogen, TGF-alpha, EGF, and insulin.
Antiestrogens, TGF-beta, and glucocorticoids inhibit its secretion [17].

Currently available additive therapies include androgens, progestins, gona-
dotropin-releasing hormone (GnRH) agonists, corticosteroids, and estrogens.
Androgens, which were discovered to be effective in the 1940s, cause tumors
to regress in approximately 20% of patients but are poorly tolerated because
of virilization and other major toxicities. Physiologic doses of estrogen (hor-
mone replacement therapy) are generally avoided in women with breast can-