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EDITORIAL

BREAST CANCER, PRESENT AND FUTURE

Breast cancer is one of the most common types of cancer affecting women. In the European Community, 1 woman in 12 is at risk of developing breast cancer, whereas the value is 1 in 8 for the U.S.A. Of the total incidence of cancer in women, breast cancer represents 25–29% and accounts for 15–18% of the mortality. Two-thirds of the breast cancers are manifested in the post-menopausal period. Forty to fifty per cent of all patients will sooner or later die as a consequence of metastatic disease.

The great majority (95%) of breast cancers, are initially hormone-dependent, and estradiol is one of the major factors that play an important role in their development and evolution. After a period that can last for several years, the tumor becomes hormone-independent. The mechanism of this conversion is not yet established, but the discovery of "variants" of the estrogen receptor (ER) has revealed intriguing possibilities. In hormone-dependent cells, the interaction of hormone with its receptor is the basic step for eliciting a hormone response. As the cancer cell evolves, mutations, deletions and truncations appear in the receptor gene and according to recent studies these modifications are principally restricted to exons 3, 5, and 7. The ER become "non-functional" despite retention of estrogen binding, and the cell fails to respond to the hormone. This observation can explain the finding that 35–40% of patients with ER positive tumors fail to respond to treatment with antiestrogens (e.g. tamoxifen).

In addition to the usual clinical observations (tumor size, absence or presence of nodes or metastases) a series of parameters can be evaluated in samples of blood and tumor tissue in order to establish the type of cancer, as well as its prognosis and treatment option. The presence of ER and/or progesterone receptor (PR) as well as the proteins pS2 (an estradiol-regulated protein of 24 K) and p53 (a transcription factor encoded by a tumor suppressor gene), a DNA-diploid stem line, and a low S-phase fraction, indicate good prognosis and favorable response to hormonal therapy. On the other hand, high values of epidermal growth factor (EGF)-receptor, tumors expressing high S-phase values and DNA aneuploidy, elevated levels of urokinase-type plasminogen activator (uPA) and its specific inhibitor PAI-1 as well as over-expression of the oncogene HER 2/*neu* and of protein cathepsin D, indicate a poor prognosis. Other interesting parameters that are under investigation are: amplification of the oncogenes c-*myc* and *Int*-2, and of various growth factors as well as of secreted proteins (e.g. stromelysine), enzyme activities involved in estradiol biosynthesis (sulfatase, aromatase, 17β-hydroxysteroid-dehydrogenase) and tumor estrogen and estrogen sulfate concentrations.

After diagnosis and removal of the tumor or mastectomy, the patient is subjected to local radiotherapy, followed by chemotherapy (5-fluorouracil, doxorubicine, cyclophosphamide) and/or endocrine treatment. Endocrine therapy is designed to decrease levels of steroid hormones (in particular estrogens), peptide hormones, growth factors, and other trophic substances that are implicated in breast cancer growth stimulation. The antiestrogen tamoxifen, at 20–40 mg/day (for 1–5 years) is now the standard first-line therapy for post-menopausal breast cancer and is accepted as an alternative to oophorectomy in pre-menopausal patients. Objective responses as high as 25–35% have been observed with tamoxifen. Other recent endocrine treatments include the administration of LHRH analogs (Decapeptyl, Zoladex) and prolactin inhibitors (dopamine agonists) as well as somatostatin analogs which decrease growth hormone (GH) and insulin-like growth factor-I (IGF-I) levels.

Recent studies have shown that breast tumors contain high concentrations of estrogens (estrone and estradiol) and estrogen sulfates (estrone sulfate, estradiol sulfate). In post-menopausal women the levels of these estrogens are of the same order as, or higher than, those

in pre-menopausal patients. Mammary tumors also contain all the enzymes needed for the formation of estradiol (aromatase, sulfatase, 17β-hydroxysteroid-dehydrogenase). Consequently, an interesting therapeutic possibility is to inhibit these enzymes. Various aromatase inhibitors are presently available (aminoglutethimide, 4-hydroxy-androstenedione). Studies carried out with these drugs in a large number of patients have yielded promising results. Several laboratories are also studying the effects of inhibitors of the enzyme sulfatase, which converts estrone sulfate to estrone. Such investigations are of particular interest because sulfatase activity in tumors is 10–100 times greater than aromatase activity.

Further directions, discriminant evaluation of prognostic factors in breast cancer research and treatment may include exploration of the following topics:

(1) Early diagnosis (mammography, evaluation of various prognostic factors).
(2) Mechanism of evolution of hormone-dependent to hormone-independent cells (e.g. ER mutations).
(3) Tumor–stromal, tumor–endothelial and tumor–immune system interactions.
(4) Characteristics of different cell populations.
(5) A better understanding of the function of tumor gene suppressors (e.g. nm23, p53, Rb).
(6) Apoptosis and its regulation.
(7) Gene therapy.
(8) The effects of treatment with growth factor inhibitors (e.g. TGF-β), retinoids, interferons, interleukins, new pure antiestrogens, new progestagens, new aromatase inhibitors, and anti-sulfatases, as well as new chemotherapeutic agents

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