Focus on breast cancer

Jose Baselga[1,3] and Larry Norton[2]

[1]Vall d'Hebron University Hospital and Universidad Autonoma de Barcelona, 08035 Barcelona, Spain
[2]Memorial Sloan-Kettering Cancer Center, New York, New York 10021
[3]Correspondence: baselga@hg.vhebron.es

Epidemiology, incidence rates, and risk factors

Breast cancer is the most frequent malignancy among women in Western countries, with an incidence rate in the U.S. of 111 cases per 100,000 woman-years (wy) and a mortality rate of 24 deaths per 100,000 wy (Howe et al., 2001). There are an estimated 1 million new cases per year in the world, with up to 5-fold lower incidence in Eastern Asia than in Western countries, a variation probably related to environmental rather than genetic factors (Probst-Hensch et al., 2000). Established risk factors for breast cancer include:

- Age. Breast cancer incidence rates double about every 10 years, reaching an incidence of 500 cases per 100,000 wy at age 70.
- Increased hormone exposure, with early menarche, late menopause, alcohol consumption, postmenopausal obesity, and hormonal replacement therapy being associated with increased risk, and young age at first pregnancy, prolonged lactation, and physical exercise being associated with a reduced risk (Feigelson and Henderson, 2001).
- Family history of breast cancer. Risk ratios increase with increasing numbers of affected first-degree relatives.

Breast cancer incidence rates peaked in the late eighties, and have been stable thereafter. On the other hand, mortality has been decreasing, with an encouraging 3.4% annual decrease from 1995 through 1998 (Howe et al., 2001; Peto et al., 2000). This decrease in mortality may be the result of widespread mammography screening and the implementation of adjuvant therapy with tamoxifen and polychemotherapy (EBCT, 1998a, 1998b).

Conventional diagnostics and therapeutics

Breast cancer is an heterogeneous disease, and its clinical signs and symptoms depend largely on whether the disease is confined to the breast or has metastasized to adjacent or distant parts of the body. Frequent sites of metastasis include the skin, lymph nodes, contralateral breast, bones, lungs, liver, and the central nervous system. The evaluation of a breast cancer patient at the time of initial presentation includes a pathological examination of the tumor and an evaluation of the extent of disease. The pathological examination includes assessment of histologic type and grade, tumor size, axillary lymph nodes status, and hormone receptor and ErbB2 receptor status. The evaluation of the extent of disease—or clinical staging—requires a physical exam and, if clinically indicated, a selected utilization of imaging techniques ranging from conventional roentograms of the chest, abdominal sonograms, and bone radionuclide scans to more complex computed tomography (CT) scans, magnetic resonance imaging (MRI), and functional imaging such as positron emission tomography (PET). Extensive utilization of imaging techniques for initial staging and follow-up is not indicated since it does not improve survival. The extension of the disease is documented with the TNM staging system, in which T refers to the tumor, N to nodes and M to metastases (AJCC, 1997). This clinical staging system, ranging from stage I (early and localized) to stage IV (metastatic) disease, is utilized to estimate the prognosis and to select the treatment for individual patients as well as to compare the results from different treatment programs.

The primary therapy of localized—early stage I and II—breast cancer is either breast-conserving surgery and radiation therapy or mastectomy with or without reconstruction. Systemic adjuvant therapies designed to eradicate clinically undetectable microscopic deposits of cancer cells that may have spread from the primary tumor result in decreased recurrences and improved survival (EBCT, 1998a, 1998b). Adjuvant therapies include chemotherapy and hormonal therapy. Chemotherapy is usually given for 4 to 6 months in combination with different agents (polychemotherapy); the drugs most frequently used are alkylating agents (cyclophosphamide), anthracyclins (doxorubicin), antimetabolites (5-fluorouracil), and antimicrotubule agents (such as paclitaxel and docetaxel) (Norton, 2001). Adjuvant hormonal therapy with tamoxifen is beneficial in patients whose tumors express estrogen and/or progesterone receptors (EBCT, 1998a). In addition, adjuvant radiation therapy provides a better local control and may enhance survival (EBCT, 2000).

In advanced disease, in addition to the agents used in the adjuvant setting, new active cytotoxic agents include vinca alkaloids (vinorelbine), pyrimidine analogs (gemcitabine), and new antimetabolites (capecitabine) (Hortobagyi, 2000). In the hormonal therapy front, tamoxifen is a selective estrogen receptor modulator (SERM) that binds to the estrogen receptor and has antiestrogenic activity in the breast and estrogenic-like activity in the endometrium, bone, and lipid metabolism (Jordan, 2001). New SERMs with a more desirable tissue selectivity are being evaluated, as well as pure antiestrogens that result in programmed early receptor destruction (Jordan, 2001). Aromatase inhibitors that prevent the peripheral tissue conversion of adrenal androgens into estrogen have recently been shown to be superior to tamoxifen and are being incorporated into first line therapy of advanced disease (Nabholtz et al., 2000).

Key genes and pathways involved in the pathogenesis of breast cancer

Breast cancer results from genetic and environmental factors leading to the accumulation of mutations in essential genes. Genes involved in the hereditary and familial forms of breast cancer include BRCA1, BRCA2, P53, PTEN, and STK11/LKB1 (Nathanson et al., 2001). The 2 BRCA genes appear to serve as important regulators of cell-cycle "checkpoint control" mecha-

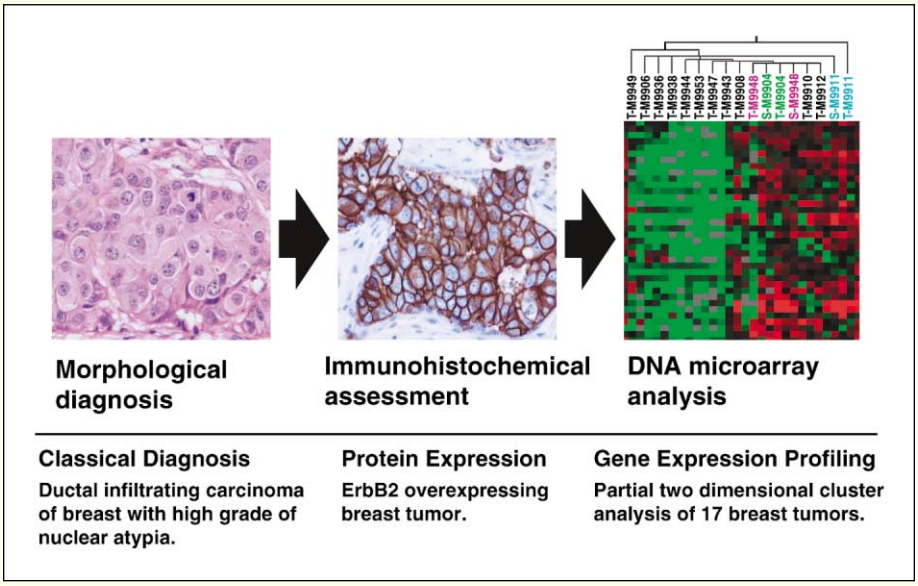

Figure 1. Evolution in breast cancer classification

The classical morphological evaluation of a breast tumor results in determination of the tumor's histological type and grade, tumor size, and number of involved axillary lymph nodes. In the last two decades, biomarkers such as hormone receptors and ErbB2 have been incorporated as prognostic and predictive factors. A third evolutionary modification may be underway with high throughput microarray technology allowing for a comprehensive molecular profiling of tumors.

nisms, involving cell-cycle arrest, apoptosis, and DNA repair. However, germline mutations of BRCA1 and BRCA2 and of these other genes account for only 15%–20% of breast cancer that clusters in families and less than 5% of breast cancer overall, and it is likely that breast cancer susceptibility may be dictated by a larger number of low penetrance mutations.

The most common genetic abnormalities in the progression of both sporadic and familial breast cancers are losses of heterozygosity (LOH) at multiple loci resulting in the uncovering of the functional consequences of mutations in alleles of tumor suppressor genes. In addition to the mentioned BRCA and P53 genes, LOH on 13q, 9p, and 16q are known to involve the Rb (retinoblastoma gene), CDKN2 (encoding the p16 protein), and CDH1 (encoding the E-cadherin protein), respectively (Dickson and Lippman, 2001). The second most common type of cytogenetic alteration is the amplification of genes, such as ErB2, c-*myc*, and cyclin D1 (Dickson and Lippman, 2001).

The role of certain receptors in breast cancer has been extensively studied, since they are either established or potential targets for therapy. The estrogen receptors are nuclear receptors that modulate transcription of target genes that play a role in the onset and progression of disease; coactivating and corepressive proteins interact with these receptors and play a critical role in the initiation of transcription (Elledge and Fuqua, 2000). Activation of tyrosine kinase receptors does also result in malignant transformation and tumor proliferation. Good examples of tyrosine kinase receptors in breast cancer are the epidermal growth factor (EGF) family of growth factors receptors, including the ErbB2 receptor, and the insulin-like growth factors and their receptors (Dickson and Lippman, 2001).

Early detection and advances in breast cancer imaging

Early detection of breast cancer is a clear priority since cure rates are greater the earlier the clinical stage at diagnosis. Screening mammography, despite an ongoing debate (Olsen and Gotzsche, 2001), is currently the best available tool for early detection, and reduces breast cancer mortality rates by about 16% for women 40–49 years old and 25%–30% for women 50–69 years old (Kerlikowske, 1997). New directions include the development of improved imaging techniques such as digital mammography and MRI. MRI may be more accurate than mammography in breast cancer surveillance of women with a hereditary risk of breast cancer (Stoutjesdijk et al., 2001). PET scanning is a functional imaging technique based on the enhanced glucose consumption by malignant cells. ^{18}F-deoxyglucose is given intravenously and is taken up preferentially by the tumor, allowing the accurate characterization of primary tumors and axillary and mediastinal lymph nodes, and also the detection of distant metastases, all in a single whole-body examination (Czernin and Phelps, 2001). PET scanning also seems well-suited to predict therapy outcome in patients with locally advanced breast cancer (Czernin and Phelps, 2001).

Advances in breast classification

The current pathologic classification and staging system are suboptimal, since patients with identical tumor types and stage of disease have markedly different responses to therapy and overall outcomes. The limitations of the current system stem from its inability to take into account biological determinants of prognosis. As a result, many patients who would have been cured by surgery and radiation therapy alone will receive unnecessary cytototoxic therapy. Over the last two decades, the routine determination of estrogen receptor and other key proteins such as ErbB2 has provided evidence that breast cancer represents several distinct subtypes (Figure 1). The advent of microarray technology with high throughput and parallel analysis of thousands of genes is allowing the linking of expression profiles to clinical outcome and response to therapy (van't Veer et al., 2002); if the predictive value of functional genomics is confirmed, it will be possible to accurately predict which tumors will relapse and to choose therapy accordingly (Ince and Weinberg, 2002). Another important implication is that molecular profiling may lead to the identification of new targets for therapy.

Recent advances in breast cancer therapy

The majority of cytotoxic agents were developed solely on the basis of their preclinical activity. However, an increased knowledge of their mechanism(s) of action is allowing the development of improved cytotoxic agents. As an example, doxorubicin inhibits topoisomerase functions, and more specific topoisomerase inhibitors are being developed; the stimulation by taxanes of tubulin polymerization has lead to the identification in tubulin polymerization screens of epothilones, active agents on taxane-refractory breast cancer (Gibbs, 2000).

In parallel, agents against a series of molecular targets that

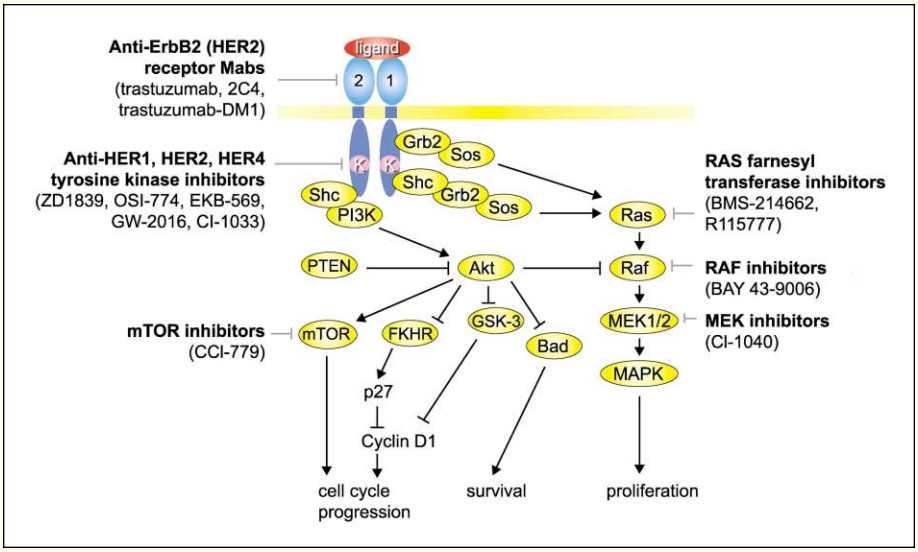

Figure 2. Advances in breast cancer treatment: Targeted therapies

The advent of targeted therapies is exemplified by a series of agents directed at the EGF receptor family of receptors and downstream-receptor dependent processes that are currently undergoing clinical trials in breast cancer. In addition to trastuzumab, other antibodies currently under evaluation include the anti-EGF receptor C225 (Baselga et al., 2000) and EMD-7200 (Bier et al., 2001), the anti-ErbB2 antibody 2C4, and monoclonal antibodies covalently bound to microtubule destabilizing agents (Schwall et al., 2001). Agents targeting receptor downstream processes include inhibitors of Ras farnesylation (Johnston et al., 2000), MEK inhibitors (Sebolt-Leopold, 2001), Raf inhibitors (Lyons et al., 2001), and mTOR inhibitors, among others (Yu et al., 2001).

dictate malignant growth are being developed. This approach is illustrated by agents directed at the EGF receptor family of growth factor receptors (Figure 2). Trastuzumab, a humanized monoclonal antibody directed at the ErbB2 receptor, is the first of this new class of agents, and is active and improves survival in patients with ErbB2 amplification (Slamon et al., 2001). Small molecules that inhibit receptor kinase activation have shown tolerability at doses that fully inhibit receptor function in vivo (Albanell et al., 2002). These agents are active in preclinical breast cancer models, and phase II clinical trials in breast cancer are ongoing.

Downstream substrates of cell surface receptors being explored as targets for therapy include the members of the Ras-Raf-MAP-kinase pathway, involved in cell proliferation, and the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR pathway that plays an important role in survival (Figure 2). Clinical responses in breast cancer have been observed with anti-RAS agents and with mTOR inhibitors. Agents are also being developed against apoptosis-regulating pathways, such as BCL-2 antisense oligonucleotides (Chen et al., 2000), proteasome inhibitors (Adams et al., 1999), and inhibitors of cyclin-dependent kinases (Senderowicz, 2000). Interactions between breast cancer cells and their surrounding environment are determinant for breast cancer progression, as exemplified by the tumor's requirement for sustained angiogenesis. Antiangiogenic agents include monoclonal antibodies targeting the vascular endothelial growth factor (VEGF), its receptors (anti-Flk-1 antibodies), and receptor tyrosine kinase inhibitors. Clinical responses in advanced breast cancer have been documented with anti-VEGF antibodies (Sledge et al., 2000).

It may be oversimplistic to expect that interfering with a single molecular target may reverse a malignant phenotype that is the result of the accumulation of multiple successive genetic events. Thus, identification of the several key drivers in a given tumor will hopefully lead to individualized treatment in which several targeted agents will be combined—tailored combination polytargeted therapy—in a rational way, rather the current empiric administration of combination polychemotherapy. In addition, as with trastuzumab and paclitaxel (Baselga et al., 1998; Slamon et al., 2001), it is expected that molecular targeting agents and cytotoxic agents will be given together in a successful partnership.

Prevention

Significant advances have been made in the field of breast cancer prevention in patients with increased risk. Studies with two different SERMs, tamoxifen and raloxifen, have demonstrated reductions in breast cancer close to 50%. (Cummings et al., 1999; Fisher et al., 1998). For women with germline *BRCA1* and *BRCA2* mutations, current management guidelines appear to reduce the risk of breast and ovarian cancer by at least 60% and 90%, respectively (Eisen et al., 2000). In a similar fashion, it is anticipated that further advances in the identification of patients with enhanced breast cancer susceptibility will allow the successful implementation of prevention strategies.

Challenges for the future

In the last two decades, major advances have been made in our understanding and treatment of breast cancer that have resulted in a decline in breast cancer mortality. To accelerate this process, research efforts need to be directed to a series of areas, including breast cancer genetics and study of populations at risk for genetic predisposition, identification of new targets for therapy and drug development programs, molecular profiling of breast tumors, and finally, improved screening and better diagnostic tools to facilitate early detection and prevention programs. However, for these advances to translate into benefit for patients, strategies to accelerate their clinical applicability have to be promoted.

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