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ADVANCES IN TARGETED THERAPY FOR BREAST CANCER (BC)

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Optimal treatment of BC includes cytotoxic and endocrine therapies, in addition to surgery and radiotherapy. Combined modality strategies have improved survival, are safe and remarkably devoid of long-term serious adverse events. Progress in our understanding of steroid hormone biology facilitated the development of novel endocrine agents. The discovery and identification of the estrogen receptor represented the watershed event in endocrine therapy. Thus, endocrine interventions became the prototype for "targeted therapy" in the area of BC. The most important lesson learned in endocrine therapy is that identification of the molecular target is critical to determine the population likely to benefit from targeted therapy. The next most important step in targeting the estrogen receptor was expanded understanding of the role of various co-factors (co-activators and co-repressors) in determining the specificity and direction of the signal. Subsequent research identified structure-function interaction in the binding pocket of the receptor and led to the development of selective estrogen receptor modulators (SERMs) and selective estrogen receptor downregulators (SERDs). Tamoxifen, the first SERM became over the past three decades the endocrine treatment of choice for all stages of hormone receptor-positive breast cancer, and the first agent with demonstrated effect of chemoprevention of breast cancer. More recent developments have highlighted the critical role of estrogen deprivation as a form of endocrine therapy. In this area, both ovarian suppression/ablation and the use of selective aromatase inhibitors have contributed to the management of breast cancer and our understanding of the differential effects of genomic and non-genomic functions of the estrogen receptor, leading to better understanding of complex cross-talk functions between steroid hormone receptors and other growth factor receptors in proliferation, survival and apoptosis of breast cancer cells. Such expanded understanding led to increasing interest in combining highly targeted molecular therapeutics to more fully interrupt critical drivers of intracellular signaling.

Research into the biological behavior of BC uncovered a number of molecular signaling processes involved in growth, proliferation, invasion and metastasis. Multiple potential therapeutic targets have been identified in recent years. Some targeted interventions were shown to have excellent efficacy and selectivity. The Human Epidermal growth factor Receptor (HER) family of receptor tyrosine kinases is one group involved in the physiopathology of some breast cancers. Members of this receptor family dimerize upon binding of natural or synthetic ligands. In the presence of substantial overexpression, homodimerization might occur without ligand binding resulting in constitutive activation of the receptor and initiation of signaling. Heterodimerization is more common, with HER-1/HER-2 and HER-2/HER-3 heterodimers being most commonly found in breast cancer. HER-2 has no known natural ligands, while HER-3 has no active tyrosine kinase domain. Thus, heterodimerization brings together complementary properties that enhance signaling and probably contributes to the specificity of signal activation. HER-1 or Epidermal Growth Factor Receptor (EGFR) is overexpressed in about 15% of BC while HER-2 is overexpressed in one out of four BC. HER-2 clearly confers malignant characteristics to the cancer cell and represents a critical driver for the malignant cell. HER-2 overexpression is almost always associated with gene amplification, and its presence confers upon the malignant cell more aggressive characteristics: increase proliferative rate, increased ability to invade and metastasize, resistance to cytotoxic drugs and some endocrine interventions and resistance to apoptosis. A monoclonal antibody directed to the extracellular domain of the HER-2 receptor, trastuzumab (Herceptin) binds with high affinity to the receptor, produces internalization of the molecule and eventually, downregulation of receptor expression. In clinical trials, trastuzumab produces objective regressions in 11% to 36% of patients with HER-2-overexpressing metastatic BC. In association with chemotherapy, trastuzumab enhances the therapeutic action of various agents, particularly the taxanes, platinum compounds, vinorelbine and the anthracyclines. In addition to increasing the response rate if individual drugs or combinations, trastuzumab results in prolongation of time to progression, response duration and survival. Prolongation of survival observed in simultaneous combinations with chemotherapy is particularly striking when compared to the sequential administration of chemotherapy followed by trastuzumab, suggesting the critical importance of temporal association between the two types of agents. While HER-2 assays (especially fluorescence in situ hybridization or FISH) identify the population likely to benefit from trastuzumab therapy, clinical trials with agents that target HER-1 failed to demonstrate the same association between target expression and therapeutic response. Clinical trials with gefitinib (ZD1839, Iressa) in advanced, metastatic BC were reported to produce an objective response in 1.7% of patients, with another 12% achieving stability. Partial responses were observed in 2% to 4% of patients treated with erlotinib (OSI-774, Tarceva). This low range of objective responses is consistent with the activity of trastuzumab in unselected groups of patients. In non-small cell lung cancer it is apparent that the presence of EGPR is insufficient to mediate response to small molecule tyrosine kinase inhibitors (TKI), and that specific activating mutations in the receptor molecule were necessary for a therapeutic response to occur. Such mutations

have not been observed in breast cancer. Rather, there is intriguing information suggesting that the interplay between activated (phosphorylated) EGFR, Akt and PTEN might select those tumors most likely to respond to trastuzumab and probably EGFR TKIs, such as gefitinib and erlotinib. There are also indications that other growth factor signaling molecules, such as the Insulin-like Growth Factor Receptor system, are integrally related to response or resistance to trastuzumab in HER-2 positive cancer cells. It is probable, then that a combination of multiple molecular markers might be needed for optimal selection of targeted treatments. Along these lines, there is increasing interest in targeting downstream signaling elements of these signaling networks. Thus, inhibitors of Farnesyl transferase, PI3 kinase, Akt, mTOR, MAP kinase, and cyclin dependent kinases are all under development. The availability of these novel agents highlighted the importance of developing molecular diagnostics simultaneously with molecular therapeutics. In addition, multiple therapeutic opportunities beg the question of the relative value of highly specific targeting of singular molecules in combination (e.g., trastuzumab plus gefitinib) versus the use of more promiscuous, multitargeted molecules (e.g., CI1033 or lapatinib).

There are multiple other cellular or tisular processes that are reasonable targets for therapeutic intervention. The process of programmed cell death, or apoptosis, is a reasonable target, since most anticancer agents act by eventual activation of this pathway. Neovascularization or angiogenesis is a critical survival mechanism of successful primary and metastatic tumors. While an extremely complex, multifactorial process, discrete components of neovascularization, such as VEGF and its cognate receptors, can certainly be identified, isolated and targeted with therapeutic intent. Such approaches to therapy are under active investigation. Challenges and opportunities related to the development of targeted therapies will be discussed.