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Successes and Limitations of Targeted Cancer Therapy in Breast Cancer

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Abstract

Breast cancer is not a single disease. Specific biological processes and distinct genetic pathways are associated with prognosis and sensitivity to chemotherapy and targeted agents in different subtypes of breast cancers. As a consequence, breast cancer can be classified by molecular events. A primary challenge for future drug development in breast cancer will be to distinguish genes and pathways that 'drive' cancer proliferation (drivers) from genes and pathways that have no role in the development of cancer (passengers). The identification of functional pathways that are enriched for mutated genes will select subpopulation of patients likely to be sensitive to biology-driven targeted agents. The selection of driver pathways in resistant tumors will permit to discover a biology-driven platform for new drug development to overcome resistance. We are moving in the era of stratified and personalized therapy. Personalized cancer therapy is based on the precept that detailed molecular characterization of the patient's tumor and its microenvironment will enable tailored therapies to improve outcomes and decrease toxicity. However, there are numerous challenges we need to overcome before delivering on the promise of personalized cancer therapy. These include tumor heterogeneity and molecular evolution, costs and potential morbidity of biopsies, lack of effective drugs against most genomic aberrations, technical limitations of molecular tests, and reimbursement and regulatory hurdles. Critically, successes and limitations surrounding personalized cancer therapy must be tempered with realistic expectations, which, today, encompass increased survival times for only a portion of patients.

We can no longer consider breast cancer as a single disease. Several breast cancer subtypes can be defined by genetic array tools [1–3] or approximations to this classification using traditional clinical-pathological features [4–7]. Molecular subtypes have different risk factors [8, 9], natural histories [10–12] and different sensitivity to sys-

temic and targeted therapies [13–15]. The discovery of 'genetic signatures' in breast cancers can provide key insights into the mechanisms underlying tumorigenesis and might prove to be useful for the design of targeted therapeutic approaches [16]. The availability of next-generation human genomic sequencing tools and progress in sequencing and biocomputational technologies will enable genome-wide investigation of somatic mutations in human breast cancers [17] at diagnosis and during their natural history. Genomic sequencing studies focus on the comparison between the sequences found in tumor samples and those of the originating normal tissues or those in the metastatic site of disease. The goal of such comparisons is to identify regions of the genome that differ frequently enough to warrant further investigation for potential causal mechanisms. Also, such studies have the potential to highlight underlying mechanisms of metastasis and resistance to drugs.

Breast cancer arises as the result of clonal expansions driven by cells that acquire a selective survival advantage through specific mutations. Genome-wide sequencing studies will therefore identify two specific types of mutations: the 'drivers' – those providing a survival and proliferation selective advantage – and the 'passengers' – those neutral to the selection process [18, 19]. One of the major goals of the analysis of data from genome-wide sequencing studies is the ranking of genes based on the likelihood that they may be drivers. This a new way in representing the 'wiring diagram' of breast cancer [20] identifying all molecular pathways that emphasize the heterogeneity and complexity of human breast cancer, explain mechanisms sustaining proliferation hallmarks of cancer and 'drive' tumor progression and resistance to chemotherapy and targeted agents. Identification of 'druggable' targets within these pathways represents a challenging platform for new drug discoveries in patients with breast cancer (fig. 1).

Molecular characterization of breast cancer subpopulation and molecular screening tools allowed the discovery of multiple oncogenic molecular alterations. A large number of such oncogenic events occur in a small percentage of breast cancer patients and define a specific segment of the disease. Disease segmentation in rare molecular entities is also related to a combination of frequent events [21]. Identification of such molecular events may be crucial to understand molecular mechanisms inducing resistance to first-line therapy. Molecular screening of pathways upregulated in resistant tumors will have a major implication in early drug development.

Luminal A and B Breast Cancer: New Targeted Therapies for the Treatment of Endocrine-Resistant Disease

Endocrine therapy is probably the most important systemic therapy for hormone receptor-positive breast cancer. Hormonal manipulation was the first targeted treatment employed in breast cancer therapy even before the role of the estrogen (ER) and progesterone receptors (PR) had been elucidated. A substantial proportion of pa-

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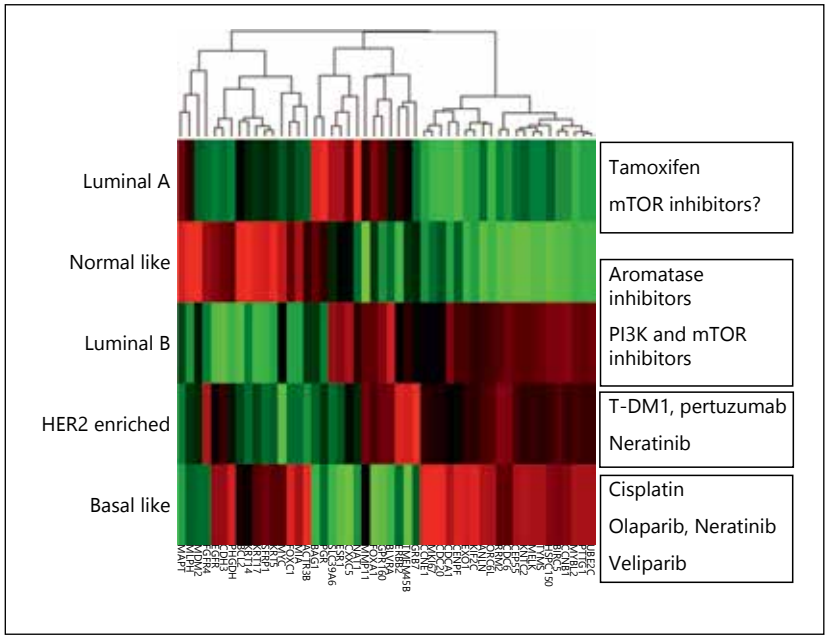

Fig. 1. New and old targeted agents for molecular subtype of breast cancer: targeting pathways to overcome resistance.

tients, despite being ER and/or PR positive, are either primarily resistant to hormone therapies or will develop hormone resistance during the course of their disease. Signaling through complex growth factor receptor pathways which activate the ER is emerging as an important cause of endocrine resistance. Hundreds of new targeted agents in pipeline are actually in development for targeting several signaling pathways in patients with endocrine-resistant breast cancer. Resistance to endocrine therapy can be related to loss of ER expression [22], to ER level decreases over time; gradual loss of E dependence [23], to upregulation of several transcriptional pathways associated with the expression of high HER2 or epidermal growth factor receptor (EGFR) [24], and several other pathways. We are faced with several challenges to personalized cancer medicine: (a) understanding the genetics of each cancer; (b) need to match the right drug with the individual tumor; (c) monitor the response to treatment; (d) design of rational combinations; (e) testing new anticancer agents earlier in disease (neoadjuvant setting). In patients with endocrine responsive disease a 'real time' testing of tumor tissue for genotype sequencing would be ideal. Early drug response and development of acquired resistance should be monitored by repeat biopsy of the tumor or, noninvasively, by functional imaging or circulating tumor cell analysis [25]. We will highlight ongoing clinical trials with signal transduction inhibitors in combination with hormonal manipulation as a means to overcome endocrine resistance in patients with breast cancer.

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Targeting Epidermal Growth Factor Receptor Pathway

Several early clinical trials have been conducted with the EGFR tyrosine kinase inhibitors (TKIs) gefitinib or erlotinib either alone or in combination with endocrine therapy. Results from the monotherapy phase II studies with gefitinib in patients with advanced breast cancer were relatively disappointing [26–28]. Two other phase II studies explored the potential benefit for combining either gefitinib or erlotinib with an aromatase inhibitor in unselected patients with ER-positive advanced breast cancer with very low clinical efficacy [29, 30]. In the setting of neoadjuvant therapy for ER-positive postmenopausal breast cancer, a randomized trial of anastrozole alone or in combination with gefitinib given for 3 months prior to surgery showed no improvement in tumor response rate or antiproliferative effect as determined by Ki-67 [31]. On the other hand, a preoperative trial of gefitinib versus gefitinib combined with anastrozole for 4–6 weeks prior to surgery in women with ER+ EGFR+ primary breast cancer reported that combined treatment induced the greatest reduction in tumor cell proliferation [32]. A double-blind placebo-controlled phase II trial of tamoxifen with or without gefitinib was conducted in 290 patients as first-line endocrine therapy in postmenopausal women with ER-positive metastatic breast cancer (MBC) [33], with an increase in progression-free survival (PFS) from 8.8 to 10.9 months (hazard ratio 0.84, 95% confidence interval, CI: 0.59–1.18, p = 0.31) [33]. A second randomized trial of gefitinib and anastrozole versus anastrozole alone in a similar first-line patient population of women with ER positive advanced breast cancer reported a prolongation of PFS from a median of 8.2 months with anastrozole to 14.6 months with the combination (hazard ratio 0.55, 95% CI: 0.32–0.94) [34]. A second randomized phase II trial with the same combination of gefitinib and anastrozole did not show any statistically significant benefit [35]. Table 1 summarizes major clinical trials with anti-EGFR-targeted agents.

Targeting HER2 Pathway

A phase II clinical trial of letrozole and the monoclonal antibody trastuzumab in patients with ER+/HER2+ MBC demonstrated a clinical benefit rate (partial response and stable disease) of 50% [36]. Subsequently, the randomized phase II TAnDEM trial in patients with ER+/HER2+ MBC reported a better PFS with the addition of trastuzumab over anastrozole alone (4.8 vs. 2.4 months, p = 00.0016) [37]. Other trials have been conducted with lapatinib, a potent oral TKI of both EGFR and HER2. Lapatinib has been explored in combination with endocrine therapy within a phase III trial of 1,286 patients with metastatic ER+ breast cancer who were randomized to receive either letrozole alone or letrozole combined with lapatinib [38]. In patients with known ER+/HER2+ breast cancer, the addition of lapatinib to letrozole significantly

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Table 1. Clinical trials combining endocrine therapies with biological targeted agents (anti-EGFR and anti-HER2) in ER-positive breast cancer

Clinical setting	Trial phase	Intervention	Clinical end points	Reference
MBC	phase II (n = 15)	anastrozole and gefitinib	response rate no response no stable disease	[29]
	phase II (n = 150)	letrozole and gefitinib	clinical benefit 11/20 patients	[30]
Early breast cancer	phase II randomized (n = 206)	anastrozole vs. gefitinib plus anastrozole	response rate 61% anastozole vs. 45% (combination arm), p = 0.067	[31]
MBC	phase III randomized (n = 207)	anastrozole vs. trastuzumab plus anastrozole	PFS 2.4 months (anastrozole) vs. 4.8 months (anastrozole plus trastuzumab), p = 0.0016	[37]
MBC	phase III randomized (n = 219)	letrozole vs. letrozole plus lapatinib	PFS 3.0 months (letrozole) vs. 8.2 months (letrozole plus lapatinib)	[38]
MBC	randomized phase II (n = 150)	tamoxifen vs. tamoxifen plus gefitinib	PFS 8.8 months (tamoxifen) vs. 10.9 (tamoxifen plus gefitinib)	[33]
	randomized phase II (n = 206)	anastrozole plus gefitinib vs. anastrozole	PFS 14.6 months (anastrozole plus gefitinib) vs. 8.2 (anastrozole)	[34]

reduced the risk of progression (hazard ratio 0.71, 95% CI: 0.53–0.96, p = 0.019) and improved the median PFS from 3.0 months for letrozole to 8.2 months for the combination [38]. The double targeting of ER and HER2 may be effective in tumors with endocrine resistance and/or established coexpression of both receptors; this promising strategy of coblockade has now become clinical reality with the recent approval of the combination of lapatinib with letrozole in HER2-positive MBC patients. Table 1 summarizes major clinical trials with anti-HER2 agents.

Targeting Phosphatidylinositol 3-Kinase/AKT/Mammalian Target of Rapamycin Signaling Pathways in Endocrine-Resistant Breast Cancer

The phosphoinositide-3 kinase (PI3K) pathway has been identified as an important target in breast cancer research. PI3K pathway is frequently aberrantly activated in breast cancer with mutations occurring in up to one quarter of endocrine-resistant breast cancer [39]. Several agents targeting the PI3K pathway are currently under de-

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