Challenges in the Treatment of Triple Negative and HER2-Overexpressing Breast Cancer

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Abstract—While the 5-year survival rate of breast cancer is at an all-time high of 90%, this disease remains the second most common cause of cancer-related death, surpassed only by lung cancer in the US. The reasons for this discrepancy stem from cancer subtypes which become resistant to current therapies. These subtypes: “Triple negative” and ErbB2-overexpressing, are discussed in this review.

Keywords — Breast Cancer, Resistance, Triple negative, ErbB2, Estrogen receptor.

I. INTRODUCTION

BREAST cancer (BC) is the most common malignancy in females and the second most common cause of cancer-related death in developed countries. In 2013 alone in the United States, an estimated 234,580 women will be diagnosed diagnosed with invasive BC and 40,030 will die from this disease (1). However, the 5-year survival rate for breast cancer patients has greatly increased in recent years and is currently about 90%. To understand this phenomenon, we must observe breast cancer subtypes as a small subset of cancers (e.g. “triple negative” and ErbB2/HER2-positive) account for a disproportionate number of deaths in women with this disease. We will report on these breast cancer subtypes and the newest therapies designed to treat them in this review.

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II. ERBB2/HER2-POSITIVE BREAST CANCERS

A. The Biology of ERBB2/HER2 overexpressing Breast Cancer

Human epidermal growth factor receptor 2 (ERBB2/HER2) is amplified and/or overexpressed in approximately 15-20% of breast cancers (2,3). Indeed, HER2-overexpressing breast cancer yields a poor patient prognosis because of a high incidence of metastases, disease progression, and resistance to current chemotherapy regimens, especially in patients whose cancers develop resistance to trastuzumab (2,4-8). Amplification or overexpression subsists in the accumulation of HER2 at the plasma membrane, which subsequently leads to the chronic activation of HER2 intracellular survival signaling pathways, thereby promoting metastatic characteristics such as proliferation, survival, motility, and invasion in breast tumor cells (9). Of these pathways, the non-receptor tyrosine kinase Src, STAT, PI3K, and MAPK pathways are the best characterized in mediating HER2 responsiveness; hence, HER2-induced over-activation of these pathways is a key component driving metastasis of this breast cancer subtype.

Proposed mechanisms for enhanced HER2 levels ultimately rest on the inadequate degradation of the protein. Unlike the epidermal growth factor receptor (EGFR) whose ligand-activated endocytosis and intracellular trafficking has become a model for all receptor tyrosine kinases, HER2 avoids delivery to lysosomes and subsequent proteolysis and is largely recycled back to the plasma membrane for reactivation (10,11). Numerous studies suggest that endocytosis impairment coupled to enhanced recycling is the cause of HER2 overexpression (12). In general, blockade of HER2 ligand-binding, dimerization, and/or HER2 intracellular signaling are the current focus for therapies in HER2-positive breast cancer.

B. Current Therapies for ERBB2/HER2 Overexpressing Breast Cancers

The current therapeutic approach for HER2-positive early-stage and metastatic breast cancer is a combination of HER2-targeted monoclonal antibody (Trastuzumab) treatment concurrent with chemotherapy (Docetaxel or Vinorelbine). The mechanism of action for Trastuzumab has not been completely established, but is perceived to be through both innate and adaptive immunities (13). Innate mechanisms lead to cell cycle arrest and adaptive mechanisms involve antibody-dependent cell-mediated cytotoxicity (ADCC) (13). Alone, Trastuzumab does not seem to promote a significant
level of cell death, but the synergistic outcome with chemotherapy results in the inhibition of the cell survival promoting PI3K/Akt signaling pathway (14,15). Additionally, the small molecule dual inhibitor of EGFR(ERBB1)/ERBB2(HER2) receptors, Lapatinib, is also FDA-approved as a combination treatment with Capecitabine for HER2-positive advanced breast cancer that has progressed after previous treatment with other chemotherapeutic agents or combination therapies (e.g. Trastuzumab/Docetaxel). Lapatinib exerts anti-proliferative effects via the inhibition of tyrosine kinase phosphorylation, which decreases the signaling capabilities of the PI3K/Akt and MAPK pathways (15).

Although both Pertuzumab and Trastuzumab bind to HER2, they bind at different locations and function through different mechanisms. Currently, the hypothesis is that the co-localized binding on HER2 may inhibit dimerization and possibly higher oligomerization with neighboring receptors or other HER2-containing complexes (19). Other modes of resistance to current HER2 therapies reside in the activation of compensatory downstream HER2 signaling pathways (17).

Based on our current understanding of HER2-overexpressing breast tumors and therapy resistance, it is possible that combination therapies that target multiple arms within HER2 function could be less likely to acclimate and develop resistance. Therapeutic interventions following this paradigm may have a higher possibility of decreasing recurrence and providing a progression-free survival. However, our current focus for anti-HER2 therapies is centered on blocking HER2 function, while abrogating the abundance or overexpression of HER2 may prove to be a more fruitful direction. Interestingly, Trastuzumab- emtansine (T-DMI) was FDA-approved in 2013 for the treatment of patients with HER2-positive, metastatic breast cancer who previously received treatment. This antibody-drug conjugate is approved for use as a single agent and promotes HER2 degradation and disruption of HER2-induced intracellular signaling (20). Several new and exciting HER2 targeting therapeutics and strategies are in clinical trials or soon to be in clinical practice (Table 1); however, there is still a considerable deficit in our understanding of the mechanisms that regulate HER2 expression and degradation.

III. TRIPLE NEGATIVE BREAST CANCERS

A. The Biology of Triple Negative Breast Cancers

Triple negative breast cancers (TNBCs) are highly heterogeneous and exhibit considerable overlap with basal-like and BRCA-mutant breast cancers (21,22). Negative for the estrogen receptor, progesterone receptor and HER2 overexpression, these cancers are quite varied in their response

<table>
<thead>
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<th>Type of Intervention</th>
<th>Identifier</th>
<th>Combination</th>
<th>Status</th>
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<tr>
<td>HER2 dimerization inhibitors</td>
<td>Pertuzumab</td>
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<td>Trastuzumab Docetaxel</td>
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<td>HER-CD3 / Anti-HER2 antibody</td>
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<td>NCT00251433</td>
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<td></td>
<td>Lapatinib</td>
<td>NCT00272987</td>
<td>Paclitaxel/ Trastuzumab</td>
</tr>
</tbody>
</table>

Table 1: Summary of Current Clinical Trials Targeted to ERBB2-Overexpressing Breast Cancers

C. Resistance Concerns and Future Directions for anti-ERBB2 Therapeutics

Unfortunately, 60% of metastatic breast cancers that express HER2 do not respond to the current anti-HER2 therapies available to patients (5-8). While several drugs targeting HER2 have proven effective for some, many patients fail to respond to treatment or become resistant. For example, a phase 3 clinical trial for Trastuzumab/Lapatinib combination treatment has provided significant benefits to patients with few side effects; 50% of patients respond to combined therapy, whereas only 32-43% with Trastuzumab alone (16). While this anti-HER2 dual approach does provide some progress in the treatment of HER2-positive breast cancer treatment, there is still a large percentage (50%) of patients that do not respond at all.

The major mechanisms of intrinsic or acquired resistance for HER2 therapies include: 1) Expression of HER2 isoforms or altered targets; 2) Increase ligand binding; and 3) Alterations in downstream signaling pathways (17). The expression of alternative isoforms of HER2 has become a common hypothesis for the lack of response or early resistance with respect to HER2 monoclonal antibody therapies. Another mechanism proposed to contribute to Trastuzumab resistance is formation of EGFR/HER2 and HER2/HER3 heterodimers (17,18). In an attempt to overcome this resistance, clinicians are assessing the use of multiple ERBB2 antibodies in clinical trials (e.g. Trastuzumab/Pertuzumab combination therapy) (Table 1).
to treatment, affect younger women, and usually have an aggressive phenotype with poor prognosis (21-23).

TNBCs account for 15-20% of all breast cancers and have a higher rate of distant metastases. Indeed, women with TNBC have a 60% reduction in their 5-year survival rate (1,24). Thus, it is vital to understand the mechanisms that lead to metastasis in the triple negative subtype of breast cancer, which is a major barrier to the eradication of this disease.

TNBC patients initially respond better to chemotherapies than non-TNBC patients, but have a poorer prognosis due to the highly metastatic nature of this cancer subtype as well as the lack of a durable treatment (23-25). If the cancer is eradicated prior to metastasis, patients often achieve excellent outcomes.

### B. Current Standard of Care for Triple Negative Breast Cancer

Triple negative breast cancers are unique in the sense that many of the most effective second-line therapies target the estrogen or the HER2 receptors, which are not present in this disease. Treatment options are limited and recurrent tumors often develop resistance to current standard therapies such as anthracyclines or taxanes. Although the mitotic inhibitor Eribulin has shown some survival benefit in metastatic TNBC patients (26,27), median increase in survival was only 1.5 months, which is far from ideal. The anti-microtubule Ibexapilone has also recently been approved for the treatment of metastatic breast cancer and has induced a significantly longer progression-free survival time when combined with capecitabine (4.2 months) than capecitabine alone (1.7 months; 28). Despite these advances, cytotoxic chemotherapy and DNA damaging agents continue to be the most frequently used for treatment of TNBC (26,29).

### C. Future Therapies for Triple Negative Breast Cancer

Targeted agents that have been or are being investigated in the treatment of metastatic TNBC include inhibitors of
poly(ADP-ribose) polymerase, angiogenesis, mammalian target of rapamycin, epidermal growth factor receptor, HDAC, and Src. Several of these agents have shown some benefit in pre-clinical trials (30). EGFR inhibitors in particular have shown promise in clinical trials in a subset of patients with the addition of either carboplatin or cisplatin (31,32). Indeed, multiple EGFR antibodies and small molecule inhibitors are currently in phase II trials. Unfortunately, a disappointing 20% of patients have so far been shown to benefit from EGFR inhibition, but this therapy may be beneficial to some patients.

Inhibitors of Src and PARP (although showing promise in pre-clinical/early phase trials) have generally not shown a distinct survival benefit as single agents for patients with TNBC (33, 34). Inhibitors for c-MET, androgen receptor, mTOR, PARP and EGFR either as single agents or in combination with other therapies have shown pre-clinical and/or early clinical promise and are currently undergoing clinical trials as either adjuvant or neoadjuvant therapies (See Table 2).

D. Novel Therapies for the Prevention of Breast Cancer

Although multiple clinical trials are currently ongoing for TNBC, pre-clinical and clinical evaluation of therapeutics for the prevention of TNBC is also currently underway. For example, recent studies of the retinoid X receptor ligands (rexinoid) class of drugs in combination with anti-estrogen modulators have shown some efficacy in the prevention of mammary tumors in murine models (35,36). Other inhibitors studied for the prevention of breast cancer include celecoxib and its derivatives (studies were halted due to increased incidence of heart attack), the selective estrogen receptor modulator (SERM) Raloxifene (NCT00003906, in clinical trials), metformin (NCT01579812, in clinical trials), and atorvastatin (Lipitor, NCT00637481, in clinical trials; 37,38,39).

IV. CONCLUSIONS

The most challenging obstacle faced by patients with HER2 expressing tumors remains overcoming either inherent or developing drug resistance in these tumors. Hence, therapies targeted towards alleviating the HER2 overexpression, combined with inhibitors to other arms of the HER2 pathway may be among the most effective future strategies.

Whereas overcoming resistance against anti-HER2-targeted therapy is of acute importance for patients with HER2-positive breast cancer, patients with the triple negative form of this disease suffer from a lack of any effective targeted therapeutic options whatsoever. The development of safe and effective therapies for the treatment of TNBC is proving to be quite challenging and is exacerbated by drug resistance, drug toxicity and the inherent heterogeneity of TNBC tumors. In this regard, inhibition of the epithelial growth factor receptor is an effective therapy for a subset of patients, but most do not benefit. Thus, the development of novel targets and combinations are of utmost importance for TNBC patients. Eradicating TNBC will likely require a more personally targeted strategy than the ones thus far tested.

REFERENCES


