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Molecular Heterogeneity of Triple Negative Breast Cancer

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Abstract

Triple-negative breast cancers (TNBCs) are known to be an aggressive group of breast cancers with higher rates of relapse stage for stage compared to ER/PR positive and HER2 positive breast cancers despite optimal loco-regional and systemic therapies. To date, not a single targeted therapy has been approved for the treatment of TNBC, and cytotoxic chemotherapy remains the standard systemic treatment. Recently, gene expression analyses identified six distinct TNBC subtypes, each displaying a unique biology. In this review we will discuss current and upcoming therapeutic strategies exploring novel approaches to targeted treatment of these TNBC subtypes.

Keywords

Triple negative breast cancer; TNBC; gene expression profiles; targeted therapy

Introduction

The approximately 15% of invasive breast cancers that lack the expression of estrogen and progesterone receptor (ER/PR) and HER2 (ERBB2) are known as “triple negative breast cancers” (TNBCs). Clinically, TNBCs are known to be an aggressive group of breast cancers with higher rates of relapse stage for stage compared to ER/PR positive and HER2 positive breast cancers. Despite optimal systemic chemotherapy, fewer than 30% of women with metastatic breast cancer survive five years, and virtually all women with metastatic TNBC will ultimately die of their disease. Vast improvements in disease free and overall survival have been made in patients with non-TNBCs, largely due to the development of drugs that target the unifying alterations in these tumors, namely the expression of ER/PR and overexpression of HER2. Drugs such as trastuzumab, pertuzumab, ado-trastuzumab, fulvestrant, tamoxifen, and aromatase inhibitors all have improved progression free and/or overall survival by targeting their respective receptors. The mainstay of treatment for

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Conflict of Interest
Vandana G. Abramson and Ingrid A. Mayer declare no conflict of interest.

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TNBC, however, remains cytotoxic chemotherapy. The benefits of targeted therapies have largely eluded TNBCs precisely because the heterogeneity of the disease has not allowed for the development of drugs to target this entire subset of breast cancer. In this review, we discuss the current understanding of the heterogeneity of TNBCs and clinical studies being undertaken to target this disease.

Understanding the diversity of TNBC

The diversity of breast cancer as a whole was characterized in the seminal paper published by Perou et al. that categorized breast cancer into distinct “intrinsic subtypes” based on gene expression profiling (1). Most TNBCs classify to the “basal-like subtype,” which is characterized by lack of ER/PR/HER2 expression and increased expression of cytokeratins 5/6, 14, and 17, P-cadherin, p53, and EGFR (2–6). Mutations and genomic deletions in *TP53* and pRB are common in this subtype, along with high proliferation indices (7–9). Although the majority of TNBCs are basal-like, approximately 20–30% of clinical TNBCs are not basal-like by microarray analysis, and a significant number of basal-like breast cancers express ER/PR or HER2 (10–12).

Several more recent studies have helped to refine our understanding of TNBCs. The Cancer Genome Atlas (TCGA) Research Network analyzed primary breast cancers using six platforms including genomic DNA copy number arrays, DNA methylation, exome sequencing, messenger RNA arrays, microRNA sequencing and reverse-phase protein arrays (13). TCGA examined the genomic heterogeneity of tumors by integrating information across platforms. The most frequent loss-of-function alterations in TNBC noted by TCGA analysis involve genes associated with DNA damage repair, including loss of *TP53, RB1*, and *BRCA1* function (13). Aberrant activation of the phosphatidylinositol 3-kinase (PI3K) signaling pathways was also frequent, thought to be secondary to the loss of negative regulators such as the lipid phosphatases PTEN or INPP4B (14, 15) or activating mutations in PIK3CA (16), along with other genes in the PI3K/mTOR signaling network (2, 16). Further support that TNBCs exhibit heterogeneity, possibly from their inception, comes from a study in which over 100 TNBCs were sequenced and analyzed at the time of diagnosis. High rates of *TP53* mutations were found, but 12% of cases did not have somatic mutations in any established “driver” genes (17).

Subtyping TNBC

Distinct subtypes of TNBC were recently identified using gene expression (GE) analyses (18), termed “TNBCtype.” Each subtype has a unique biology, and in *in vitro* studies, responds optimally to different therapies. The TNBCs subtypes, include two basal-like TNBC subtypes, one with cell cycle and DNA damage response GE signatures (BL1) and the other enriched in growth factor signaling and myoepithelial markers (BL2), two mesenchymal subtypes with high expression of genes involved in differentiation and growth factor pathways (M and MSL), an immunomodulatory (IM) type, and a luminal subtype driven by androgen signaling (luminal androgen receptor, LAR) (18). Furthermore, TNBCtype was used to identify TNBC cell lines that were representative of these subtypes. “Driver” signaling pathways were pharmacologically targeted in these cell lines as proof-of-concept and to generate pre-clinical data to inform future clinical trial design.

A recent retrospective analysis of correlation of pathologic response rates from 130 TNBCs treated with neoadjuvant doxorubicin, cyclophosphamide, and paclitaxel and the different TNBC subtypes by TNBCtype GE expression was performed by Masuda et al (19). The highest pCR rate (52%) was seen in the BL1 subtype, while the BL2, LAR and MSL subtypes were found to have the lowest response rates (0%, 10%, and 23%, respectively). TNBCtype was also shown to be an independent predictor of pCR status ($p = 0.022$) by a likelihood ratio test (19). Such findings suggest that patients with TNBC should be aligned to different therapies based on their disease subtype.

Targeting basal-like TNBCs

Platinum Salts—Numerous similarities have been noted in tumors arising in BRCA1 carriers and basal-like sporadic breast tumors, including greater likelihood of being ER/PR-negative, HER2-negative, and a high frequency of p53 mutations (20). Basal keratins are expressed by both sporadic basal-like tumors and tumors with *BRCA1* mutations, and both groups cluster together by gene expression profiling (20). Like *BRCA1* mutated tumors, basal-like TNBCs are notable for EGFR expression, *c-MYC* amplification, *TP53* mutations, loss of RAD51-focus formation, genomic instability and sensitivity to DNA-crosslinking agents (21).

The DNA damage response GE signatures seen in BL1 TNBCs provide further evidence of the similarity of this subtype to BRCA1 mutated breast cancers and signal ways to target BL1 TNBCs. Platinum salts, including carboplatin and cisplatin, lead to DNA cross-link strand breaks, which may be especially important in cells which are deficient in homologous recombination repair mechanisms such as BRCA mutated cells and BL1 TNBCs.

Clinically, initial evidence of the activity of platinum agents in TNBC has been demonstrated in two phase II studies. Silver et al. showed activity of neoadjuvant cisplatin as a single agent in the treatment of 29 patients with locally advanced TNBCs. The observed pathologic complete response (pCR) was 22%; 50% of patients had a partial response and 14% had a complete response (22). In another small study, 9 of 10 patients with stage I–III breast cancer harboring BRCA1 mutations achieved a pathological complete remission after neoadjuvant therapy with cisplatin (23).

Further evidence of the activity of platinum agents in TNBC comes from two large phase II randomized trials in the neoadjuvant setting: the GeparSixto phase II randomized trial, in its TNBC subset, compared neoadjuvant paclitaxel, liposomal doxorubicin, and bevacizumab to the same regimen with the addition of carboplatin. The pCR rate improved from 37.9% to 58.7% with the addition of carboplatin. However, only about 50% of patients were able to complete treatment due to adverse events (possibly since all chemotherapy drugs were given concomitantly) (24). CALGB40603 (NCT00861705) is a randomized phase II trial with a 2 × 2 factorial design that explored the addition of carboplatin +/− bevacizumab to neoadjuvant weekly paclitaxel followed by dose-dense AC in in 443 patients with stage II/III TNBC (25). The pCR rate improved from 41% to 54% with the addition of carboplatin; bevacizumab had no added benefit.

While the GeparSixto and CALGB40603 phase II trials cited above have clearly shown the merit of adding a platinum agent to the systemic treatment of patients with TNBC in the neoadjuvant setting, these trials were clearly underpowered to address disease-free (DFS) and overall survival (OS). The pooled analysis performed by Cortazar et al. (26) could not validate pCR as a surrogate endpoint for improved event-free survival (EFS) and OS in patients with TNBC. There are several possible reasons for this: the improvement in pCR could simply represent a marginally improved response on a subject already destined to do well, and the incremental benefit of certain interventions is overall small. It should also be noted that some patients who achieve pCR go on to relapse, and many with residual disease never experience a recurrence. Variability will always be introduced by other factors, including the negative effect of high-risk clinical variables even in patients achieving pCR, and the positive results of effective drugs given in the adjuvant setting. Ultimately, the reason to treat patients in the (neo)adjuvant setting is prevention of distant recurrence and death from breast cancer. An improvement in pCR rate is certainly encouraging; however, it may not always translate into a DFS and OS improvement. Therefore, studies that are adequately powered to detect a DFS and OS form the addition of platinum agents to standard of care chemotherapy are still important and needed. It may be, however, reasonable to consider the addition of a platinum agent in the neoadjuvant setting for patients in whom an increase in clinical response to systemic treatment could improve loco-regional control (i.e. patients with triple-negative inflammatory breast cancer, or inoperable TNBC at diagnosis).

PARP inhibition—The poly(ADP-ribose) polymerase 1 (PARP1) enzyme mediates the base excision repair pathway and is critical for the repair of single-strand DNA breaks. In *BRCA* mutated cells, the PARP enzyme is of particular importance as these cells are unable to rely on homologous recombination to repair DNA breaks. Inhibition of PARP1 by RNA interference or with chemical inhibitors leads to severe, highly selective toxicity in *BRCA1* and *BRCA2*-defective cells (27). Sensitivity to PARP inhibition depends on homologous recombination deficiency and not necessarily on inherited *BRCA1* or *BRCA2* deficiency (28). PARP1 inhibitors may therefore be an effective therapeutic strategy in the treatment of sporadic breast cancers with “BRCAness,” including basal-like breast cancers.

Iniparib is not a typical PARP inhibitor, and investigations into potential targets of iniparib and its metabolites are still ongoing. An initial phase II report of gemcitabine/carboplatin with or without iniparib in patients with metastatic TNBC was promising, since the reported clinical benefit rate improved from 33.9% to 55.7% (p=0.015) and ORR from 32.3% to 52.5% (p=0.023) with the addition of iniparib. Interestingly, a significant improvement in median progression free survival (PFS) from 3.6 to 5.9 months (hazard ratio [HR], 0.59; p=0.012) and the median overall survival (OS) from 7.7 to 12.3 months (HR, 0.57; p=0.014) (29) were also seen. However, the confirmatory phase III study which had an almost identical design, did not meet its endpoints for OS and PFS (30). Around that same time, a single arm phase II study of neoadjuvant gemcitabine, carboplatin, and iniparib in patients with TNBC or BRCA 1/2 mutation associated breast cancer was initiated(31). A homologous recombination deficiency (HRD) assay was developed as part of this study to identify non-BRCA1/2 mutation carriers with “BRCA-like” cancers who may benefit from

DNA repair-targeted treatment strategies. Patients that were *BRCA* 1 and 2 carriers and patients with higher HRD scores were the ones with the higher rates of clinical and pathologic complete response.

The PARP inhibitor olaparib was shown to have significant single agent activity in patients with BRCA-deficient metastatic breast cancer. Overall responses ranged from 22% (100 mg bid) to 41% (400 mg bid) with minimal toxicity (32). A phase II study evaluating olaparib as a single agent for patients with either recurrent high-grade serous or poorly differentiated ovarian carcinoma or TNBC (33), did not report any responses in the patients with TNBC. Several phase III trials investigating the use of olaparib in the metastatic and neoadjuvant setting, for patients with BRCA mutations, are ongoing.

The I-SPY2 trial uses an adaptive study design to treat breast cancer in the neoadjuvant setting; based on the molecular characteristics (biomarker signatures) of a tumor, drugs under investigation are combined (and compared) with standard anthracycline-and taxane-based chemotherapy to identify novel treatment regimens for different breast cancer subsets. One of the first mature results is from a trial of the combination of standard chemotherapy with and without veliparib, a PARP inhibitor, and carboplatin, for stage II and III patients with TNBC (34). The primary endpoint of the study, the rate of pCR at the time of definitive surgery, was significantly improved by the addition of veliparib and carboplatin (52% vs. 26%). However, it is unclear if the addition of veliparib to carboplatin contributed in any way to the increase in pCR rate, since the combination results are quite similar to what was seen with the addition of carboplatin only in the GeparSixto and CALGB40603 neoadjuvant trials; definitive studies are underway.

PI3K inhibition—Phosphatidylinositol-3 kinase (PI3K) inhibition may also be relevant for basal-like tumors, despite the fact that less than 20% of TNBCs harbor mutations in the PI3K pathway (35). Preclinical studies of a DNA damaging agent with PI3K inhibitors have provided rationale for using PI3K inhibitors in non-LAR tumors by demonstrating that in addition to regulating cell growth, metabolism, and survival, PI3K also stabilizes double strand breaks by interacting with the homologous recombination complex and, in effect, creating a BRCA deficient state (36). PI3K blockade promotes homologous recombination deficiency by down-regulating BRCA1/2, creating a BRCA mutant-like tumor state and thus sensitizing BRCA-proficient tumors to PARP inhibition. A phase I study of the pan-PI3K inhibitor BKM120 (Novartis®) in combination with the PARP inhibitor olaparib, for patients including those with metastatic TNBC is under way (NCT01623349).

Similarly, our studies of combinations of PI3K-inhibitors and cisplatin show either additive or synergistic decreases in tumor viability, with significant decreases in pAKT and pS6 levels and a concomitant elevation in cleaved PARP. Therefore, we are now conducting a clinical trial in which patients with androgen receptor-negative metastatic TNBC are randomized to chemotherapy with cisplatin with or without a PI3K inhibitor (NCT01918306).

Targeting Luminal Androgen Receptor TNBC

The LAR subtype of TNBC comprises only 10% of all TNBCs, and is characterized by androgen receptor signaling, along a high rate of *PIK3CA* activating mutations. In preclinical studies, the LAR subtype exhibits a strong pre-clinical additive/synergistic sensitivity to PI3K inhibitors and to androgen blockers (18). Patients with this subtype could potentially be spared from the toxicity of a chemotherapy regimen with expected limited benefit by capitalizing on the potential targets: the PI3K pathway and the androgen receptor. This will be explored clinically in a phase I/II study of an androgen blocker with a PI3K inhibitor for patients with AR+ TNBC expected to activate in the second quarter of 2014.

Conclusion

TNBC is a heterogeneous and complex disease, and should not be treated in a uniform fashion. Numerous experimental approaches seek to identify “targets” in TNBC: PI3K inhibitors, MEK inhibitors, HSP-90 inhibitors, histone deacetylase inhibitors, and PD-1 (programmed death 1) inhibitors, are a few of the agents under consideration or currently being investigated in the clinical setting against this disease. For the majority of targeted therapies in development, there are still no clinical tools to determine which patients are most likely to benefit or, alternatively, be resistant *de novo* to these novel agents or drug combinations. The study of biomarkers of drug exposure and sensitivity in metastatic tumors, although feasible, is not easy due to the inherent difficulty of obtaining sequential tumor samples only for research purposes. Testing novel agents for TNBC in the neoadjuvant or post-neoadjuvant setting is so attractive precisely because the tissue collected at the time of definitive surgery would be enriched with a tumor clone that could be studied for mechanisms of therapeutic resistance.

Ultimately, combining two or more targeted agents with or without chemotherapy may be required for a more rational and optimal approach to TNBC treatment, since combination of “complementary” pathway inhibitors would potentially maximize efficacy, and would minimize therapeutic resistance. TNBC subtyping is one of the first steps in the direction of guiding the differential use of novel regimens and alignment of patients with select TNBC subtypes to clinical trials investigating targeted therapies.

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