

Update on triple-negative breast cancer: prognosis and management strategies

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Abstract: Triple negative breast cancer (TNBC) is a heterogeneous disease comprehending different orphan breast cancers simply defined by the absence of ER/PR/HER-2. Approximately 15%–20% of all breast cancers belong to this phenotype that has distinct risk factors, distinct molecular features, and a particular clinical presentation and outcome. All these features will be discussed in this review. The risk of developing TNBC varies with age, race, genetics, breastfeeding patterns, and parity. Some TNBC are very chemo-sensitive and the majority of patients confronted with and treated for TNBC will never relapse. Some (histological) subgroups of TNBC may have good prognosis even in the absence of chemotherapy. Distinct molecular subgroups within TNBC have been defined now as well. In case metastatic relapse occurs, this is usually within 5 years following surgery, and survival following metastatic relapse is shorter compared to other breast cancer subtypes; treatment options are few and responses lack durability. Novel drug targets and new biomarkers are needed to improve breast cancer care for patients presenting with TNBC. Further molecular/biological unraveling of TNBC is needed.

Keywords: breast cancer, triple negative, review

Introduction

Breast cancer remains the most frequently diagnosed female cancer worldwide and the leading cause of cancer death, despite screening and improvements in adjuvant treatment.^{1,2} Breast cancer is a clinical heterogeneous disease encompassing about 15 different types of carcinomas, which are for therapeutic reasons, further sub-classified according to their estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status. For the majority of patients, targeted therapies against one of the abovementioned targets are available. These treatment options are absent in patients diagnosed with tumors lacking ER, PR, and HER2. These breast carcinomas are therefore referred to as triple negative breast cancers (TNBC).

TNBC represent a consistent subgroup of breast cancers with heterogeneous clinical presentation, clinical behavior, histology, and response to therapy. Awareness of TNBC was recently increased by the discovery of the intrinsic molecular subtypes in breast cancers with gene expression profiling experiments. At least five molecular categories (ie, luminal A/B, HER2-like, normal breast-like, and basal-like) have been repeatedly identified in breast cancer, each with prognostic significance.³ TNBC fall mostly in the so-called basal-like subtype, however this classification system presents some limitations in regard to accuracy, interobserver variability, and costs for analysis, preventing their introduction into the clinic. Therefore, more easy to use immunohistochemical

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surrogate definitions of molecular subtypes have been implemented into international guidelines.⁴

We will discuss definitions, epidemiology, risk factors, clinical and pathological characteristics, and management of TNBC. We conducted a PubMed search in the English literature using the terms “triple negative”, “breast cancer”, and “basal”, and selected those articles that seemed relevant for this review.

Definitions

The terms “TNBC” and “basal-like breast cancer” are often used interchangeably, which can be confusing to the reader; however, despite the fact that most TNBC are basal-like, the two definitions are not synonymous.

The diagnosis of TNBC is an immunohistochemical orphan definition, characterized by the lack of expression for ER, PR, and HER-2.⁴ However methodological inconsistencies and use of different definitions for determining ER, PR, and HER2 status yield different results in phenotyping TNBC worldwide.^{5–10} The joint American Society of Clinical Oncology (ASCO) and College of American Pathologist (CAP) guidelines for the assessment of ER, PR, and HER2 will likely result in a better standardization.¹¹ Furthermore, the use of a 1% threshold for ER and PR positivity will most likely reduce the proportion of cases diagnosed as TNBC.¹¹ Adherence to these guidelines is crucial since false negative/positive results for ER, PR, and HER2 have been reported to occur in up to 15%–20% of patients, potentially leading to unjustified withholding of endocrine treatment (undertreatment) or unnecessary overtreatment (cytotoxic chemotherapy) in some patients.^{12,13}

The existence of breast cancers expressing myoepithelial-specific cytokeratins (also known as basal cytokeratins) dates back to the second half of the 80s.^{14,15} However, it was only after the molecular revolution introduced by the seminal work of Perou et al that the term basal-like came into widespread use.³ Thus, the term basal-like refers to a molecular definition, and describes those tumors that, at the transcriptomic level, show a profile similar to that encountered in basal/myoepithelial cells of the normal breast (ie, expression of mRNA of basal keratins). Because of the complexity and the cost of gene expression profiles, a number of studies have provided diverse immunohistochemical surrogate definitions for basal-like breast cancers.^{16–20} Immunohistochemical introduction of basal cytokeratins (CK5 and CK6) and/or epidermal growth factor receptor 1 (EGFR1) can identify up to 81% of basal-like breast cancers in one series.¹⁹ Further addition of CK14 and 17 has also been proposed.²¹ The lack of a standardized

immunohistochemical panel, and standardized cut-off values to identify basal-like breast cancers within TNBC hampers its clinical usefulness. Currently the term “basal-like breast cancer” in diagnostic pathology reports does not lead to any clinical direct action and therefore is best avoided, unless for prognostic purposes.

A remarkable discrepancy between immunohistochemical and molecular classification of breast carcinomas is often observed. Although approximately 40%–80% of TNBC will cluster in the molecular basal-like compartment, around 20%–60% will be allocated to other intrinsic phenotypes (ie, Luminal A, Luminal B, Luminal-HER2, HER-2 like, claudin-low, normal-breast like), with different biology.^{18,22–26} For example, claudin-low breast cancers are a TNBC subtype biologically closely related to mammary stem cells (poorly differentiated) that may be enriched in BRCA pathway alterations.²⁷ They have low expression of genes involved in tight cell junctions (including E-cadherin), almost always have an intense immune infiltrate, and often exhibit features of epithelial–mesenchymal transition.²⁷ Vice versa, molecularly defined basal-like breast cancers might show immunohistochemical expression of ER, PR, and/or HER2 in a substantial number (20%–40%) of cases.^{28–30} New data have recently emphasized that the molecular complexity within TNBC constitutes more than basal versus non-basal TNBC.³¹ Recent transcriptome analysis from a large number of TNBCs from 21 independent studies identified six stable and biologically different clusters of TNBC exhibiting unique gene expression patterns and gene ontologies.³¹ These include two basal-like clusters (enriched in cell cycle and DNA damage response genes), two mesenchymal-like clusters (enriched in cell differentiation, epithelial–mesenchymal transition, and growth factor pathways), an immunomodulatory cluster (enriched in cell surface antigens, receptors, and signal transduction genes), and a luminal cluster (driven by androgen receptor signaling).³¹

Epidemiology and risk factors

The risk of developing TNBC varies with age, race, genetics, waist/hip ratio, breastfeeding patterns, and parity. Several population-based studies have shown that TNBC often presents at a younger age and more frequently in African American women and black ethnicities.^{18,32–35} A large study of the California Cancer Registry revealed that women with TNBC are significantly more likely to be aged < 40 years, that non-Hispanic black (compared to white) women are twice as likely to be diagnosed with TNBC, and that the incidence of TNBC was twice as high as the incidence of

other breast cancer subtypes.³² In the Carolina Breast Cancer Study, the prevalence of TNBC or basal-like breast cancers was 39% in premenopausal and 14% in postmenopausal African American women (compared with 16% in non-African American women).^{18,36}

In hereditary breast and ovarian cancer syndromes, there is a well-established association between deleterious BRCA-1 mutation status and the risk of developing TNBC.³⁷ BRCA-1 is a tumor suppressor gene involved in double-strand DNA break repair and BRCA-1 deficiency results in higher genomic instability and tumor genesis. The lifetime risk of developing breast cancer in patients with hereditary breast and ovarian cancer syndromes may be as high as 50%–85%, but the risk greatly varies depending on the patient's age, hormonal status (first age at menarche, etc), familial/genetic predisposition, and breast density.³⁸ As few as five single nucleotide polymorphisms can modify breast cancer penetrance from 95% down to 45%.³⁹ Up to 75% of breast cancers developing in BRCA-1 carriers are TNBC, basal-like, or both.^{40,41} Young age at breast cancer diagnosis, and/or medullary (or medullary-like) histology and high mitotic activity (above 100 mitosis in ten high power fields) may hint towards BRCA-1 mutational status.⁴²

Patients younger than 50 years diagnosed with TNBC but lacking a specific familial predisposing history are carriers of BRCA-1 mutations in 10%–30% of cases.^{43,44} This observation may be important for the elaboration of genetic testing guidelines.⁴⁵ Furthermore, a considerable (20%) proportion of TNBC patients without the somatic BRCA-1 mutations may still have impaired DNA repair mechanisms due to other abnormalities in the BRCA pathway,^{46–52} (also referred to as BRCA-ness; ie, loss of heterozygosity of genomic regions encompassing these genes, BRCA-1 promotor methylation). The specific genomic instability in BRCA-1 (and 2) carriers may provide specific therapeutic opportunities (ie, platinum-type drugs that generate double-stranded DNA breaks or poly (adenosine diphosphate ribose) polymerase (PARP) inhibitors that prevent repair of single-strand DNA breaks).

Interestingly, although regarded as an endocrine insensitive disease, several hormonal alterations throughout a woman's life are associated with an increased risk of developing TNBC. Parity and young age at first full-term pregnancy increase the risk of developing TNBC but breastfeeding, a longer duration of breastfeeding, and an increasing number of children breastfed, all reduce the risk of developing TNBC.³⁶ Some studies did not find an association between parity and breast cancers being more likely to be TNBC.^{53,54} A higher waist/hip ratio is associated with an

increased absolute risk for developing TNBC irrespective of menopausal status.³⁶

Clinical and pathological presentation

TNBC usually presents at ages younger than that at which population-based organized breast cancer screening programs are offered. The majority of patients diagnosed with TNBC will therefore present with a palpable tumor. Among woman attending population-based organized breast cancer screening, TNBC will more likely present as an interval cancer (between two organized mammography screening rounds).^{55,56}

Radiological features of TNBC are variable, although several reports describe typically a well-circumscribed mass, absence of spiculated margins, absence of microcalcifications, and/or an echogenic halo.^{57–59} High malignant intensity signals are characteristic both on magnetic resonance imaging or positron emission tomography. In one study, 18 patients with TNBC received positron emission tomography with F-18 fluoro-deoxyglucose and all tumors exhibited focally enhanced uptake, suggesting high sensitivity of positron emission tomography in TNBC.⁶⁰

Histologically, TNBC are heterogeneous, being mostly invasive ductal carcinomas of no special type. In about 90% of the cases, TNBC are poorly differentiated with high proliferative activity and large primary tumor size.^{18,23,61} Microscopically, TNBC frequently show pushing borders associated with central necrosis, and a variable degree of lymphocytic infiltration.^{40,41} High-grade TNBC often present a dismal prognosis.

Special types of TNBC include medullary, metaplastic, secretory, adenoid cystic, invasive lobular carcinomas, apocrine/histiocytoid carcinomas, and carcinomas arising in microglandular adenosis. Recognition of special types of TNBC is of utmost importance since some of them are associated with better prognosis and indolent clinical course, such as adenoid cystic and secretory carcinoma. These low-grade TNBC (as compared to high-grade TNBC) carry relatively simple genomes and are characterized by specific chromosomal translocations resulting in chimeric fusion genes. The *ETV6-NTRK3* and *MYB-NFIB* fusion genes have been recently described in secretory and adenoid cystic carcinomas, respectively.^{62,63} In Azoulay's series (n = 18, median follow-up 6.5 years, one patient died of disease) adenoid cystic TNBCs had excellent outcomes even in the absence of adjuvant chemotherapy, and on reviewing the literature (n = 219 adenoid cystic TNBC cases), they found a 3% breast

cancer specific death rate, although information on adjuvant treatment was lacking.⁶⁴ Despite the histological features of classical medullary carcinomas (ie, highly proliferative, poorly differentiated carcinomas), these tumors frequently carry a good prognosis. In a series of medullary carcinomas ($n = 41$), high radiosensitivity was suggested (7% of the patients had a complete response after a dose of 55–60 Gy) and chemotherapy had no effect on the rate of recurrence or survival (6-year local recurrence-free survival, metastasis-free survival, and survival rates were 86%, 83%, and 83%, respectively).⁶⁵ Another series of medullary carcinomas ($n = 71$), also presented with good outcomes (10-year distant metastasis-free survival of 81.4%) with chemotherapy only given to a minority ($n = 11$).⁶⁶ Good outcomes (14-year distant recurrence-free interval of 89% for ER-negative medullary breast cancer) were also noticed in the International Breast Cancer Study Group (IBCSG) ($n = 127$), but almost 70% received adjuvant chemotherapy.⁶⁷ High-grade metaplastic carcinomas may be resistant to systemic cytotoxic therapy and are associated with poor prognosis while low-grade metaplastic breast cancers may have better prognosis (ie, fibromatosis-like carcinoma).^{68,69}

The relation between TNBC and lymph node status is less clear. Some authors found no relation, others found a negative association, and some found a positive association.^{40,55,70–72} Whatever the relation between TNBC and lymph node status, the lack of a relationship between increasing tumor size and lymph node involvement in TNBC suggests that these breast cancers preferentially spread hematogenously, giving rise to metastatic deposits in brain and lungs.⁷³

Prognosis and prognostic variables

The discovery of the intrinsic breast cancer phenotypes was associated with differences in outcome and there is a unique recurrence pattern for “basal-like” and TNBC compared to other phenotypes, such as ER-positive tumors.^{3,55} Relapse rates are particularly high during the first years following surgery with a peak recurrence risk 3 years post-surgery in TNBC; afterwards, the recurrence risk rapidly declines.⁵⁵ By contrast, in ER-positive breast cancers, more than 50% of recurrences are recorded between 5 and 10 years after the first surgery.⁷⁴ In the long term, TNBC have intermediate outcomes, and more events will occur in high-grade ER-positive breast cancers.^{24,74,75}

Whether TNBC is associated with an increased risk for locoregional relapse remains debatable, but some data suggest that both TNBC as well as HER-2 overexpressing breast cancers are at increased risk for locoregional relapse, also

following mastectomy.^{76–78} The risk of developing subsequent distant metastasis and death following locoregional recurrence is higher in TNBC compared to other subtypes.⁷⁹

Survival after metastatic relapse is shorter in TNBC compared to other subtypes. In part, this can be understood from the predilection for visceral and lung metastasis compared with ER-positive breast cancers that are more likely to relapse in bone and skin.^{75,80,81} Women with TNBC are at increased risk of developing brain metastasis (10%–30% depending on whether autopsy reports are considered) and median survival after brain metastasis is shorter compared with patients developing brain metastasis from other breast cancer phenotypes.^{82–84}

The prognostic value of classical pathological variables such as tumor grade, lymph node status, and tumor size, could be impaired in TNBC. Indeed, most TNBC are high grade, and first generation prognostic molecular assays, which are driven mainly by proliferation, did not show prognostic value in TNBC.⁸⁵ In contrast, Ki67 stainings in TNBC have been suggested to carry prognostic information in some reports but not in others.^{86,87} Small (cT1a/b) node-negative TNBC are potentially aggressive as well.⁸⁸ Despite the abovementioned issues, the Nottingham Prognostic Index (NPI) has been reported to be useful in TNBC.⁸⁹

Many other pathological prognostic variables (ie, lymphovascular/perivascular invasion, androgen receptor, e-cadherin) have been studied, mainly in retrospective cohorts, and therefore their use in daily clinic is not recommended.^{90–93} Interestingly, the recently reported molecular heterogeneity within TNBC might be concordant with some of these previously reported pathological variables. As such for example, Claudin-low TNBC seem to express less e-cadherine, some TNBC show an androgen signalling pathway whereas others mainly show an immune signature.^{31,94} In the past already, tumor lymphocyte infiltration in TNBC has been associated with more favorable prognosis before.^{22,95} Furthermore, an immune response gene module has been correlated with achieving pathological complete remission (pCR) in ER-negative breast cancer.⁹⁶

Many studies have demonstrated the association between pCR and good prognosis, but the prognostic value of pCR was recently shown to be limited to certain breast cancer subtypes only (ie, TNBC, non-Luminal HER2-like, and Luminal B [HER2 negative]).⁹⁷ Allowing no residual tumor burden in breast nor in lymph nodes provided superior prognostic information compared to other definitions.⁹⁷ Anthracycline or anthracycline–taxane-based regimens in TNBC allow achieving pCR rates up to 20%–45% and these patients exhibit

excellent prognosis, comparable with non-TNBC patients (achieving pCR).^{80,97–100} Although adjuvant treatment remains the gold standard, neoadjuvant treatment can be considered to downstage large TNBC or lymph node-positive TNBC, and for patients willing to participate in neo-adjuvant trials exploring the efficacy of novel (additional) drugs. These trials use pCR as a substitute outcome variable, although it remains to be determined what increments in pCR (like recently shown by adding bevacuzimab [Avastin®; Roche-Genentech, Basel, Switzerland] to standard chemotherapy) translate into improved survival.^{97,101}

Ethnicity has also been reported an independent prognostic variable with black women having inferior prognosis.^{18,32} The prognostic role of histology and lymph node status has been discussed earlier in this manuscript.

Treatment Locoregional

Locoregional treatment of TNBC is no different than for other invasive breast cancers. Although surrogate basal-like breast cancer and TNBC have been suggested to have inferior 10-year locoregional outcomes compared to other subtypes, there are no surgical implications, since it was found to be true both following breast conserving surgery and mastectomy.^{76–78} Breast-conserving surgery remains the standard in small cT1 and some cT2 breast cancers compared to mastectomy for larger tumors, multifocal/multicentric tumors, and in cases of involved section margins after previous breast-conserving surgery. Women with large TNBC may achieve higher rates of pCR following neoadjuvant chemotherapy, allowing breast-conserving surgery.^{80,98–100} Guidelines for adjuvant radiotherapy are no different than in other breast cancer subtypes. One specific consideration regarding locoregional treatment in TNBC is the option for prophylactic surgery in patients with BRCA-1 mutations.

Chemotherapy in the (neo-)adjuvant setting

Chemotherapy is the only systemic treatment to improve disease outcomes following the diagnosis of a TNBC, since a target is missing. TNBC can be highly sensitive to chemotherapy, as demonstrated by high rates of pCR following neoadjuvant chemotherapy.^{80,98–100}

In the adjuvant setting, there is no proof that some chemotherapeutic agents are superior to others in function of a particular breast cancer.¹⁰⁰ Anthracycline/taxane-based regimens constitute today's standard regimen for patients not participating in clinical trials.¹⁰² Previously, anthracycline-containing

regimens have demonstrated their superiority compared to cyclophosphamide, methotrexate, and fluorouracil-containing regimens also in TNBC adjuvant trials.^{103,104} Later, addition of taxanes to an anthracycline-based regimen resulted in improved disease-free survival and overall survival, independently of ER expression.^{105,106} Anthracycline/taxane-based chemotherapy regimens have been shown to be highly active also in TNBC.⁹⁸

As previously stated, the specific genomic instability in BRCA-1 carriers may provide specific therapeutic opportunities in TNBC. Platinum salts (ie, cisplatin) bind to DNA, causing DNA cross-linking. These double-stranded DNA breaks elicit DNA repair mechanisms (homologous recombination or nonhomologous end joining).^{102,107} The lack of this repair mechanism in BRCA-1 (and 2) mutant patients (that are frequently TNBC) turns cells into apoptosis rather than repair. Striking pCR rates (72%–90%) have been reported in BRCA-1 mutation carriers following single-agent cisplatin neoadjuvant treatment, but the number of patients included in these studies was limited (n = 10 and n = 25) or data were retrospective in nature (n = 102).^{108–110} In non-BRCA-1 mutant TNBC, the efficacy of platinum remains a subject of further study. Unfortunately, a larger and randomized Phase II trial (n = 94 TNBC patients) could not find an increased pCR rate following the addition of carboplatinum to an anthracycline/taxane-based regimen.¹¹¹

Chemotherapy in advanced TNBC

Metastatic relapse in TNBC is associated with a paucity in treatment options through the absence of ER/PR/HER-2. Although discordances in receptor status between the primary breast tumor and the metastatic lesion have been reported for ER, PR, and HER-2, few patients with TNBC will gain extra treatment options.¹¹² Confirmatory biopsies of metastatic relapse in breast cancer are however, recommended. Receptor status switch may represent a change in biology, although the possibility of false-negative staining results in the primary breast cancer should be ruled out. In the prospective series of Amir et al, two of 23 women with initial TNBC were found to have receptor discordance on the metastatic biopsy.¹¹² Both represented false-negative staining and therefore true receptor discordance is an unlikely event in patients with TNBC. Reanalysis of the primary tumor in these women is recommended.

Chemotherapy remains the backbone of systemic treatment in TNBC. Since the disease has become incurable, treatment goals have become prolongation of survival and palliation of symptoms. Unfortunately, responses to systemic cytotoxic therapy lack dura-

bility, and prognosis is inferior compared to other subtypes.^{75,99} Single agent chemotherapy is generally reasonable, but combination chemotherapy may be preferred in cases where immediate response is necessary (ie, visceral crisis). In analogy with the adjuvant setting, once breast cancer is metastatic, there is no evidence that some chemotherapeutic agents are superior to others in function of a particular breast cancer subtype. Single-agent chemotherapy options in TNBC include anthracyclines (doxorubicin, epirubicin, etc), taxanes (paclitaxel, docetaxel, etc), anti-metabolites (capecitabine, gemcitabine), and other microtubule inhibitors, and/or stabilizers (vinorelbine, eribulin, ixabepilone). Platinum agents (cisplatin, carboplatin), for reasons mentioned before, may be of particular value in a subset of TNBC (those with BRCA-related dysfunctions). Several Phase II trials studied platinum salts in often heavily pretreated advanced breast cancer, showing only moderate 10%–30% response rates (irrespective of breast cancer phenotype).^{113–115} Further data in advanced TNBC are warranted. Combined chemotherapy regimens that have activity in anthracycline-pretreated patients, irrespective of breast cancer phenotype, include paclitaxel plus gemcitabine and docetaxel plus capecitabine.^{116,117} Adding ixabepilone (an antitubulin agent) to capecitabine improves response rates and progression-free survival, also in TNBC.^{118,119}

Targeted treatments

Molecular processes and biological drivers that have been targeted in TNBC include vascular endothelial growth factor (VEGF), inefficient DNA repair mechanisms (ie, PARP), the epidermal growth factor (EGFR, also called HER-1), mammalian target of rapamycin (mTOR), Src oncogene pathway, histone deacetylase (HDAC), and androgen receptor. In general, clinical introduction of these molecules is hampered by a lack of predictive biomarkers.

The therapeutic role of angiogenesis inhibitors in (TN)BC remains uncertain. VEGF is associated with poor prognosis in breast cancer generally and with shorter survival in first-line metastatic TNBC. Despite improved progression-free survival and response rates, no overall survival was seen in any of the Phase III trials (E2100, AVADO, RIBBON-1) assessing the efficacy of bevacizumab (a humanized monoclonal antibody targeting VEGF).^{120–122} The clinical relevance of the significantly improved progression-free survival should therefore be questioned and the US Food and Drug Administration approval for use of this drug in breast cancer has been revoked.¹²³ In the neoadjuvant setting, some data reveal only small clinical benefits but increased toxicity and cost from the addition of bevacizumab to cisplatin, while the addition of bevacizumab to anthracycline/taxane-based chemotherapy resulted in increased

pCR rates in the GeparQuinto study, confined to TNBC but not in the NSABP trial.^{124–126} Results from the randomized Phase III trial (BEATRICE) assessing the value of bevacuzimab in the adjuvant TNBC setting are awaited.¹²⁷

PARP inhibitors are a novel class of agents of particular interest to treat TNBC, especially in those tumors showing altered BRCA functionality. High PARP expression has been reported in BRCA-1 associated and TNBC and PARP, a nuclear protein activated in the presence of DNA damage, is highly expressed in BRCA-1 related breast cancers that most likely are TNBC. PARP activity increases following radiotherapy/Chemotherapy-induced DNA damage.^{128,129} PARP is involved in several mechanisms essential in recovering from DNA damage and cancer growth. PARP inhibitors, in monotherapy or combined with chemo and or radiotherapy are therefore promising novel drugs that may enhance chemosensitivity and radiation sensitivity by inducing lethal DNA breaks that cannot be repaired in BRCA-deficient tumor cells, eventually resulting in cancer cell death. Several PARP inhibitors are in clinical development (ie, olaparib [AZD2281; AstraZeneca, London, UK], veliparib [ABT-888; Abbott, North Chicago, IL]), with promising results in BRCA1/2-associated breast cancers of any subtype, but not so far in unselected non-BRCA-related TNBC.^{130–135} Although Phase II trials with iniparib (Sanofi-Aventis, Paris, France) found improved progression-free and overall survival with minimal toxicity, results remained unconfirmed in a subsequent larger Phase III trial.¹³⁴ Methodological issues have been suggested, but molecular heterogeneity in TNBC may explain these results as well.^{102,136}

EGFR/HER-1 is overexpressed in up to 70% of TNBC patients and has an important role in proliferation, migration, and protection against apoptosis.^{22,29,72,137} Moreover a subset of TNBC and basal-like breast cancers show *EGFR1* gene amplification or chromosome 7 aneusomy. Nevertheless, only modest or clinical non-significant activity was found by using monoclonal antibodies (ie, cetuximab [Erbix[®], ImClone, New York, NY]) against EGFR1.^{138–140} Effective selection strategies (biomarker development) are necessary to identify patients with TNBC that may truly benefit from these drugs.

Other potential targets in advanced TNBC currently being studied are mTOR, Src tyrosine kinase, and histone deacetylase (HDAC-i). mTOR is an effector of the PTEN/AKT/IP3K pathway, often dysregulated in breast cancer and can be inhibited with Everolimus (Afinitor[®], RAD001, Novartis).¹⁴¹ Src tyrosine kinases are overexpressed in basal TNBC and promote receptor tyrosine kinase phosphorylation, affecting cell adhesion and migration.¹⁴² Dasatinib (Sprycel[®], BMS-

354825, Bristol-Myers Squibb, New York, NY) is an oral, small molecule tyrosine kinase inhibitor also affecting Src active in preclinical studies.¹⁴³ HDAC-i work mainly through epigenetic mechanisms, by altering the acetylation status of the histonic proteins (that control the chromatine architecture), they influence the expression of key genes such as ER in breast carcinomas. Thus, administration of HDAC-i may result in re-expression of functional ER mRNA and protein, in ER-negative breast cancer.¹⁴⁴ A proportion of TNBC express androgen receptors and molecular studies recently distinguished a TNBC phenotype enriched in androgenic pathways.³¹ A Phase II trial assessing the value of the anti-androgen bicalutamide in metastatic TNBC is underway (NCT00468715).

Conclusion

TNBC is a heterogeneous disease comprehending different orphan breast cancers simply defined by the absence of ER/PR/HER-2. Some TNBC are very chemosensitive as can be seen from neoadjuvant data, and the majority of patients confronted with and treated for TNBC will never relapse. Those patients experiencing metastatic relapses usually do so within 5 years following surgery. Metastatic survival is shorter compared to other subtypes, and treatment options are few and responses lack durability. Novel promising drug targets are being studied, but the discovery of reliable predictive biomarkers is imperative before these novel treatments can be translated into the clinic. Molecular studies are teaching us that TNBC constitutes different biological diseases.

Disclosure

All authors report no conflicts of interest in this work.

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