Triple Negative Breast Cancer: A Review of Clinicopathologic Characteristics And Treatment Options

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Abstract: Breast cancer is the second leading cause of cancer death in women. Approximately 15-20% are triple negative breast cancer (TNBC: no protein expression of estrogen receptor, progesterone receptor, nor human epidermal growth factor receptor 2), representing one of the most challenging molecular subtypes of breast cancer. TNBC encompasses a heterogenous group of breast cancers that are not generally responsive to targeted therapies for hormone and growth factor receptors. Compared to their hormone receptor-positive counterparts, TNBC cases are associated with poor prognosis, worse overall survival and earlier recurrence. The purpose of this review is to describe the clinicopathologic features, molecular variants, associations with the BRCA genes, and therapeutic approaches for TNBC. New TNBC-targeted drug therapies are currently under investigation and include poly-ADP-ribose polymerase (PARP) inhibitors, platinum-based drugs, anti-epidermal growth factor receptor (EGFR) inhibitors, and anti-vascular endothelial growth factor receptor (VEGF) inhibitors. Both clinical trials and basic research are needed to further our understanding of the best treatment options for patients with TNBC.

Keyword: Triple negative breast cancer.

INTRODUCTION

Breast cancer is the second leading cause of cancer death in women. Reports from the American Cancer Society estimates that the incidence of breast cancer in 2013 for the United States is 122 per 100,000 women, with a mortality rate of 23 per 100,000 [1]. New pharmacotherapeutics, increased awareness, and early detection have resulted in decreased mortality, with a 5-year overall survival of 90% today, compared to 75% survival in the mid-1970s [1]. Breast cancer is a complex and heterogeneous condition; the molecular characteristics that define a breast cancer impact treatment selection and prognosis. Tailoring therapy based on molecular subtypes of breast cancer has markedly improved clinical outcomes [2, 3]. However, the "triple negative" phenotype has been difficult to target and is associated with poor survival.

"Triple Negative Breast Cancers" (TNBC) are comprised of heterogeneous breast cancers, defined broadly as breast cancers that lack protein expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal factor receptor 2 (HER2) by immunohistochemistry (IHC). TNBC accounts for approximately 15-20% of newly diagnosed breast tumors [4, 5]. Due to differences in pathologic interpretation, the definition of TNBC may vary. One problem that contributes to the confusion is the discrepancies in the IHC cutoffs (<1% or <10%) applied to determine ER and PR status [6-8]. Additionally, discordance

between determinations of HER2 positivity achieved by IHC or by fluorescence in situ hybridization (FISH) has been documented [8, 9]. Accurate determination of the HER2 status is crucial since this marker is used not only for treatment selection but also as a prognostic tool. To address these issues, the American Society of Clinical Oncology (ASCO) and the College of American Pathologist (CAP) have issued guidelines to standardize the parameters used to determine ER, PR, and HER2 positivity. For ER and PR positivity, current guidelines recommend a threshold ≥1% of immunoreactive cells [6]. Recommendations for HER2 positivity by IHC is >10% (3+) evidence of protein expression in tumor cells, or by FISH, where over-expression of HER2 is determined by the ratio of the copy number over the number of evaluated nuclei in at least 20 cells. Specific recommendations on tissue fixation and selection of antibodies are important since these factors have led to variability in results [10]. Overlap with BRCA1 germline mutation carrier is another confusing subject. Most BRCA1 mutation carriers are triple negative and have a basal-like phenotype; however, their clinical management may differ from the non-BRCA1 mutant TNBC patient. The purpose of this review is to describe the clinicopathologic features and therapeutic approaches associated with TNBC.

BREAST CANCER MOLECULAR SUBTYPES

Patient prognosis are determined by clinical-pathologic factors such as age, race, menopausal status, family history, stage at diagnosis, tumor histology, and immunohisto-chemical stains for ER/PR status and HER2 expression. About 75-80% of the breast cancers are hormone receptor positive. In general, when compared to hormone receptor positive tumors, TNBC have a higher proliferation rate (54%

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vs 17%) [11, 12]. Over the past decade, gene expression profiling and their correlation to immunohistochemical markers have led to the identification of different molecular subtypes of breast cancer: luminal A, luminal B, HER2 positive, and basal-like [4, 13, 14].

With regard to overall survival, significant differences exist between the four molecular subgroups. Luminal A breast cancers originate from cells lining the mammary ducts, are ER/PR positive and HER2 negative, and have the longest relapse-free and overall survival (OS) [15]. Also derived from the luminal cells of mammary ducts, Luminal B tumors may have lower ER/PR expression, but are HER2 positive. HER2 positive tumors are ER/PR negative with overexpression of the HER2 gene, and are usually associated with poor prognosis [5]. Basal-like breast cancers are derived from the basal layer of the breast; they have a high nuclear proliferation rate [5, 16]. Basal-like tumors are ER/PR negative, but express basal cytokeratin 5/6 and 17. The majority of basal-like tumors harbor a tumor suppressor TP53 mutation [5]. Basal-like and HER2-positive subtypes have the shortest relapse-free and OS [13]. In a study by Montagna *et al*. [15] using a large cohort of patients (n=8801), including 781 TNBC, the 5-year disease free survival (DFS) for TNBC is 77%, compared to 68% for the HER2+, 95% for the Luminal A and 84% for the Luminal B subtypes. The 5-year OS was 83% for TNBC, and 94% for HER2-positive, 98% for the luminal A and 94% for the luminal B.

Basal-Like Molecular Subtype

The basal-like molecular subtype is a subset of TNBC. While TNBC is simply defined by IHC/FISH staining criteria, no clear consensus exists to define basal-like breast cancer [8, 16]. About 77% of the basal-like tumors are TNBC; and among the TNBC, 70-80% are basal-like [8, 17, 18]. Commonly, basal-like tumors are characterized by the presence of basal markers such as epidermal growth factor receptor (EGFR), cytokeratins (CK) 5, CK6, CK14, CK17, p-cadherin, p63, c-kit, and smooth muscle actin [19-23]. Lehmann *et al*. [24] have used gene expression profiling to characterize TNBC using data from 587 TNBC. They define 6 subtypes of TNBC: basal-like 1 (increased cell cycle genes, DNA damage response genes, and overexpression of Ki-67 mRNA, suggesting increased sensitivity to taxanes); basal-like 2 (high expression of TP63); immunomodulatory (presence of profuse immune infiltrate, immune cell-surface antigen expression, and cytokine signaling); mesenchymal (overexpress genes involved in cell motility); mesenchymal stem-like (upregulation of genes associated with motility, angiogenesis, and stem-cell associated genes); and luminal androgen receptor subtype (increased gene expression of androgen receptors) [24]. Other investigators have proposed different subclassifications, such as luminal C, claudin-low, and C-kit [23-26]. The claudin-low subtype has a mesenchymal phenotype and is characterized by decreased cell-to-cell junction proteins like claudin and E-cadherin, as well as the presence of prominent immune infiltrates [23]. However, these molecular descriptions and their response to targeted therapies require further study and validation.

BRCA1/2 Mutations

Germ-line mutations in the BRCA1 and BRCA2 gene confer an increased lifetime risk of breast cancer since these genes are involved in DNA repair and maintenance of genomic integrity [27]. The Consortium of Investigators of Modifiers of BRCA1/2 analyzed 3,797 BRCA1 and 2,392 BRCA2 mutation carriers, reporting that 69% of BRCA1 mutation carriers had invasive TNBC, compared to only 16% of patients with BRCA2 mutations [28]. Also, TNBC and BRCA1 mutation were independently associated with younger age at diagnosis, as well as higher grade and stage tumors when compared with non-TNBC [28, 29]. BRCA1 carriers commonly express basal markers and are of the basal-like subtype [28]. The BRCA1 mutant subtype is present frequently in women of Ashkenazi Jewish heritage and is associated with a family history of breast and/or ovarian cancer. In contrast, African-American women more commonly have sporadic, non-BRCA-associated TNBC [29].

Identification of the BRCA1 mutation among patients with breast cancer has been used as a prognostic factor and as a tool for treatment selection [27]. Patients with BRCA1 mutations have been shown to have good response to DNA damaging agents such as platinum salts and poly-ADP-ribose polymerase (PARP) inhibitors [30, 31]. Rather than a mutation inactivating the gene, "BRCAness" can be achieved *via* epigenetic promoter methylation, leading to dysfunctional BRCA1 gene expression [29, 32-34]. These TNBC tumors may also respond well to platinum agents and PARP inhibitors [34].

Histologic Subtypes of TNBC

The histologic subtype for the majority of TNBC is invasive ductal carcinoma (IDC) (89%); other histologic subtypes include apocrine (4%), lobular (2%), adenoid cystic, metaplastic, papillary and medullary, which account for 1% of the cases. Each histologic subtype has different estimated 5 year OS: 84% for IDC, 82% for invasive lobular carcinomas, 88% for metaplastic and papillary, 92% for apocrine, and 100% for the medullary and adenoid cystic subtypes [15]. The lowest 5-year DFS is seen in the metaplastic subtype (55%), compared to apocrine (84%), IDC (77%), papillary (67%), lobular (64%), and the adenoid and medullary subtypes (100%) [15].

CLINICAL PRESENTATION AND CHARACTERISTICS

TNBC have been consistently shown to be more common in African-American women [6, 35, 36]. However, some studies have also found Hispanic women to have a higher incidence of TNBC [26, 37]. TNBC is usually diagnosed at a younger age [5, 26, 38], and presents at a higher stage and larger size when compared to the other breast cancer molecular subtypes. Most studies show that TNBC patients have poor prognosis, worse overall survival and earlier recurrence compared with their hormone receptor positive counterparts, even when the diagnosis was made at an early stage [39, 40]. Additionally, TNBC has more than 20% greater incidence of visceral metastasis compared to the other breast cancer subtypes, which commonly metastasize to bone [37, 41]. This incidence of visceral relapse decreases dramatically with long-term follow-up and are comparable to that of non-TNBC [12]. Other factors, such as menopausal status, obesity, use of oral contraceptives and their influence in the incidence of triple negativity varies among studies [42]. Since TNBC predominantly affects younger patients, it can be expected that more patients within this group are premenopausal. Further evaluation to validate the

relationship between obesity and TNBC must be done since the incidence of obesity among African-American/Hispanics women may be confounders.

TREATMENT

The lack of molecular targets identified in TNBC excludes this patient population from the benefits of endocrine or HER2-targeted therapies; therefore, standard chemotherapy in conjunction with surgery and/or radiation therapy remains the standard of care. Some radiation therapists advocate the use of post-mastectomy radiation in all patients with TNBC. The combination of radiotherapy with adjuvant chemotherapy following mastectomy, for the treatment of TNBC, showed a striking increase in the 5-year OS (90.4%) compared to patients who received chemo-therapy alone (78.7%) [41]. The 5-year recurrence-free survival (RFS) was 88% in the radiotherapy group compared to 74.6% in the chemotherapy only group [41]. The addition of radiotherapy increased the time to distant metastasis by two or more years in patients with TNBC [41].

CHEMOTHERAPY

Most of the data to manage TNBC patients are derived from retrospective subset analyses of clinical trials which include all subtypes of breast cancers, rather than prospective randomized trials for TNBC patients only. Due to the aggressive nature of TNBC, with high and early incidence of recurrence, many experts advocate the administration of chemotherapy even in the event of node negative small tumors [40]. Patients with TNBC consistently demonstrate poor prognosis when compared with other molecular subtypes of breast cancer, regardless of treatment, and despite early stage disease [39, 43]. The recurrence rate for stage I and small TNBC tumors have been reported between 12-23% and up to 46% in patients <35 years of age, compared to recurrence rates of 5% in patients with small HER2-positive cancers and 11% in small hormone positive breast cancers [39, 44].

TNBC is currently treated with anthracycline (doxorubicin, epirubicin) and taxane (paclitaxel, docetaxel) containing regimens. Docetaxel along with anthracycline containing regimens in TNBC have shown improved DFS [43, 45, 46]. Administration of 5-fluorouracil, epirubicin and cyclophosphamide followed by paclitaxel (FEC *vs* FEC-P) reduced the chances of relapse in TNBC by 47% and 67% in the basal-like phenotype with a seven-year DFS of 18% and 26%, respectively [47]. Capecitabine is an oral pro-drug that converts to 5-fluorouracil in the tumor. The Finland Capecitabine Trial studied the effect of docetaxel and capecitabine followed by cyclophosphamide, epirubicin, capecitabine (TX/CEX), compared to no capecitabine (T/CEF). Patients with TNBC (n=202) showed the greatest benefit in recurrence-free survival with TX/CEX [48]. Additionally, the classical chemotherapeutic approach, consisting of cyclophosphamide, methotrexate and 5-fluorouracil (CMF), has been shown to be beneficial for patients with TNBC [49, 50].

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is an important treatment option for patients with advanced breast cancer for two reasons: 1) reduction of tumor burden to increase possibility of breast conserving surgery, and 2) the ability to assess the tumor's response to the drug. While some studies claim improvement in long-term survival for those patients who achieved the pathologic complete response (pCR) rate following neoadjuvant chemotherapy [51, 52], others show that pCR achievement does not improve the OS for the TNBC subgroup [37, 53]. Liedtke *et al.* [37] reported the clinical outcomes of TNBC patients (n=255) who received neoadjuvant chemotherapy; the pCR was 22% compared to 11% in non-TNBC. However, the 3-year progression-free survival (PFS) was lower in TNBC (63%) than in non-TNBC (76%), and the overall survival was 74% in TNBC *vs* 89% in the non-TNBC. They concluded that although TNBC have a higher pCR rate, patients with residual disease after neoadjuvant chemotherapy have the worse survival compared with non-TNBC patients.

In the neoadjuvant setting, capecitabine with docetaxel resulted in a pCR rate of 19% in TNBC patients, compared to 3% in the non-TNBC group; however, DFS was lower in TNBC patients [54].

Metastatic Disease

Capecitabine is also a treatment option after progression of the disease in patients previously treated with anthracycline/taxane. Other non-cross-resistant agents such as gemcitabine and vinorelbine are used as single agents after failure of anthracycline/taxane in TNBC, with pCR rates ranging from 28 to 40% compared to 3-14% without gemcitabine or vinorelbine [55-57]. Epothilone B ixabepilone and Eribulin recently gained FDA approval for the treatment of advanced disease and have been shown to be efficacious in TNBC patients [58, 59].

Another strategy in the treatment of metastatic breast cancer is the metronomic administration of cytotoxic agents, whereby lower doses are administered over a longer period of time. The purpose of these regimens is to achieve longer survival with fewer side effects. For HER2 negative breast cancers, Yoshimoto *et al.* [60] found that TNBC patients had an overall response rate of 44.4% with a progression-free survival of 10.7 months; and for ER/PR-positive patients, the response rates were 46.4% and 12.2 months PFS. It has been postulated that this treatment modality induces endothelial cells apoptosis, resulting in angiogenesis impairment [60]. This is an interesting approach that merits further investigation considering the lack of durability in the patient response to chemotherapy seen in TNBC.

Examples of other strategies are sequential monotherapy *versus* the use of combination chemotherapy, high dose *vs* dose dense regimens, anthracycline rechallenge as well as diverse treatment scheduling [61-63]. Despite having shown positive effects on TNBC in some cases, further studies are required to validate the findings.

NEW TARGETED THERAPIES FOR TNBC

DNA Repair Damaging Agents

New strategies in the treatment of TNBC BRCA1 mutation carriers involve the use of PARP inhibitors. Drugs such as olaparib, veliparib, and niraparib inhibit the PARP-1 enzyme, which is needed for base excision repair in the DNA repair process. PARP inhibition, combined with loss of

DNA repair due to BRCA mutation, results in selective cell death for tumors with the BRCA1 germline mutation [64]. These drugs have been shown to be effective in patients with BRCA 1 or BRCA 2 mutation, including those with TNBC; however, these studies are in early phases and continued investigations are underway [65-67].

Iniparib, a drug with an unknown mechanism of action, was originally thought to be a PARP inhibitor. Phase II and phase III clinical trials have studied the effects of iniparib in combination with gemcitabine and carboplatin in patients with TNBC. Although the phase-II study (N= 123 TNBC patients) reported striking benefits with the addition of iniparib (overall response rate of 52% compared to 32% for chemotherapy alone, p=0.02) [67], the phase-III study (N= 519 TNBC patients) failed to show significant results in PFS and OS when compared to patients on gemcitabine and carboplatin alone [68].

Platinum-based therapy, such as carboplatin and cisplatin, bind and crosslink DNA, which selectively will target BRCA-mutated cancer cells unable to repair from DNA damage. Platinum salts for use in metastatic TNBC have been investigated in various clinical trials based on the prevalence of BRCA1 mutation among TNBC. *In vitro* studies have documented a potential marker capable of predicting platinum sensitivity in TNBC: 60 to 80% of the TNBC harbor p53 mutations; co-expression of transactivated p73 and N-terminal truncated p63 (both part of the p53 tumor suppressor family) form a protein complex unit in TNBC tumors carrying the p53 mutation. Treatment with cisplatin reactivates the pro-apoptotic activity of p73 [69]. Platinum therapies have been investigated in combination with: cetuximab [70], taxane [71], gemcitabine [72], and paclitaxel [73] with variable results. For patients with metastatic TNBC or locally advanced TNBC, treatment with a cisplatin regimen improved DFS and OS [72, 74, 75]. However, other studies of platinum-based therapies have shown limited benefit in TNBC [76, 77], and thus, no conclusive results on the benefits of platinum can be made.

Anti-Epidermal Growth Factor Receptor (EGFR)

Over 40% of the TNBC basal-like subtype overexpress EGFR, and its presence has been commonly associated with worse prognosis [16, 43, 78, 79]. Compared to hormone receptor positive tumors, patients with TNBC are 6.5 times more likely to express EGFR (7% *vs* 49%, respectively) [11]. However, a recent analysis of 253 TNBC found no correlation between EGFR expression and unfavorable long-term outcomes [11]. In a retrospective study, TNBC overexpressing EGFR had better pCR rates when compared to non-TNBC in the neoadjuvant setting; however, on multivariate analysis, EGFR expression was not an independent predictor of OS (p= 0.7) [80]. Additional studies investigating the use of EGFR inhibitors in TNBC are ongoing [78, 81, 82].

Data from clinical trials show that use of cetuximab, an anti-EGFR monoclonal antibody, only shows a moderate response rate in metastatic TNBC. Cetuximab has been investigated in combination with cisplatin, carboplatin, and carboplatin plus irinotecan, resulting in objective response rates (ORR), ranging between 18-49% with very limited effect on OS [70, 83, 84].

Lapatinib, an EGFR tyrosine kinase inhibitor that inhibits EGFR and HER2, was evaluated in several phase I and II studies. Although inhibition of HER2 was verified in tissue biopsies, there was no clinical benefit in TNBC [85, 87]. This drug seems to be more beneficial in HER2 positive breast cancer rather than HER2 negative breast cancer [88-91]. Finn *et al*. [92] reported no benefit in patients with HER2 negative breast cancer randomized to receive paclitaxel with or without lapatinib.

Other drugs known to inhibit EGFR such as vandetanib, erlotinib, and afatinib, have only modest response rates in advanced breast cancer [93-97]. Most of the studies are limited by the low number of subjects; therefore, future studies are needed to corroborate these findings [93-98]. Despite the high expression of EGFR in TNBC, inhibition of this pathway had little effect in tumor progression, suggesting that alternate mechanisms are highly activated and are yet to be discovered. A new agent, panitumumab, is currently under investigation (NCT00894504, NCT01009983) [99, 100].

Anti-Vascular Endothelial Growth Factor Receptor

Vascular endothelial growth factor (VEGF) plays an important role in tumor angiogenesis. Agents that target VEGF may represent an attractive option for TNBC, which is known for its rapid clinical progression. Bevacizumab, a VEGF inhibitor, was approved to be used in addition to paclitaxel in Europe (E2100 trial) following a phase-III randomized trial that reported prolonged PFS in patients with advanced breast cancer [101]. Thereafter, several studies have introduced bevacizumab in their treatment regimens with encouraging results in PFS and an overall response rate in HER2-negative patients [102-104].

In a randomized study with 1,948 patients who received neoadjuvant epirubicin, cyclophosphamide, followed by docetaxel, or in conjunction with bevacizumab, the rate of pCR among TNBC patients was 39.3% for those who received bevacizumab and 27.9% in those who did not [105, 106]. However, in the phase-III BEATRICE trial (n=2,591 with TNBC), when bevacizumab was administered in the adjuvant setting in addition to chemotherapy and continued for one year, DFS and OS were not different between patients who received bevacizumab with chemotherapy *versus* those who received chemotherapy alone [107].

Other studies show benefits of the addition of bevacizumab to metastatic chemotherapy regimens, such as paclitaxel [101, 103, 108], docetaxel [102], and other compounds such as erlotinib [96]. In contrast, recent reports from the Breast Avastin Trial showed that TNBC patients treated with maintenance bevacizumab following treatment with docetaxel and capecitabine did not differ in their PFS and ORR when compared with hormonal receptor positive tumors [109]. The addition of bevacizumab to current metastatic therapies has been shown to increase the risk of drug toxicities without significant long-term benefit; thus the FDA has not granted the approval of this agent to treat advanced TNBC.

Sunitinib and sorafenib are anti-VEGFR tyrosine kinase inhibitors recently used in advanced HER2 negative metastatic breast cancer patients. Results provided by several clinical trials are inconclusive [110-114]. Clinical trials with

sorafenib are currently investigating its effect on metastatic TNBC (NCT01194869) [115].

CONCLUSION

TNBC is a heterogeneous disease, and thus is challenging to treat. Definitive characterizations and appropriate treatments remain unresolved. Unfortunately, most of the clinical trials do not take into consideration the different subtypes of TNBC when reporting treatment outcomes. A study solely performed in TNBC based on the different subtypes is challenging since it may be hindered by low accrual. Understanding which treatments can benefit a particular patient cohort within the TNBC group requires further studies in correlating molecular phenotypes with specific targeted therapies.

ABBREVIATIONS

ASCO   = American Society of Clinical Oncology

CAP   = College of American Pathologist

DFS   = Disease-free survival

EGFR   = Epidermal growth factor receptor

ER   = Estrogen receptor

FISH   = Fluorescence in situ hybridization

HER2   = Human epidermal factor receptor 2

IDC   = Invasive ductal carcinoma

IHC   = Immunohistochemistry

pCR   = Pathologic complete response

PFS   = Progression-free survival

PR   = Progesterone receptor

RFS   = Recurrence-free survival

TNBC   = Triple negative breast cancer

VEGF   = Vascular endothelial growth factor

CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest.

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