Triple Negative Breast Cancer Pathological Diagnosis and Current Chemotherapy Treatment Options

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Abstract

Triple negative breast cancer (TNBC) comprises 12–20 % of all breast cancers and are a heterogeneous group of tumours, both clinically and pathologically. These cancers are characterised by the lack of expression of the hormone receptors oestrogen receptor (OR) and progesterone receptor (PR), combined with the lack of either overexpression or amplification of the human epidermal growth factor receptor-2 (*HER2*) gene. Conventional cytotoxic chemotherapy and DNA damaging agents continue to be the mainstay of treatment of this disease in the neoadjuvant, adjuvant and metastatic setting. The lack of predictive markers in identifying potential targets for the treatment of TNBC has left a gap in directed therapy in these patients. Platinum agents have seen renewed interest in TNBC based on an increasing body of preclinical and clinical data suggesting encouraging activity. However, comparisons between chemotherapy regimens are mostly retrospective in nature and the best agents or drug combinations for TNBC have not been established in prospective randomised trials. Numerous studies have now shown that TNBC has significantly higher pathological complete response (pCR) rates compared with hormone receptor positive breast cancer when treated with neoadjuvant chemotherapy, and pCR correlates well with better outcomes for these patients. Patients with TNBC account for a larger number of deaths in the setting of metastatic breast cancer. There is no preferred treatment for the first-line metastatic setting. Although individual agents are recommended, given the often aggressive nature of TNBC and the presence of extensive visceral disease, the use of a combination of drugs, rather than a single agent, is often advocated. This review article will outline the pathological diagnosis of TNBC and the treatment options available to these patients in the neoadjuvant, adjuvant and metastatic setting, including an assessment of future directions of treatment.

Keywords

Breast cancer, triple negative, pathological diagnosis, chemotherapy treatment, neoadjuvant, targeted treatment, adjuvant, metastatic

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The treatment of triple negative breast cancer (TNBC) is an unmet medical need, which refers to tumours that are oestrogen receptor (OR) and progesterone receptor (PR) negative, and where human epidermal growth factor receptor 2 (*HER2*) is not overexpressed. This subset accounts for approximately 12–20 % of breast cancer patients.[1] Gene expression analysis on this heterogenous group of patients demonstrates an overlap between the molecular signature of TNBC and basal-like (BL) breast cancer (BLBC). The concordance rates between the two groups are in the order of 70–90 %. Not all TNBC can be defined as BLBC as a small minority of BLBC patients express OR and HER2 receptors.

The purpose of this review is to discuss the pathological diagnosis, current trends in management of TNBC in the neo-adjuvant, adjuvant, and metastatic disease treatment and future directions.

Pathological Features and Diagnosis of Triple Negative Breast Cancer

TNBC, which comprises 12–20 % of all breast cancers, are a heterogeneous group of tumours, clinically and pathologically at the molecular level.[1] The defining features of this cohort of breast cancers are a lack of expression of the hormone receptors OR and PR, combined with a lack of either overexpression or amplification of the *HER2* gene. The majority (around 70 %) has been demonstrated to be BLBC, and this subtype is defined by an overexpression of epidermal growth factor receptor-1 (EGFR-1) and basal cytokeratins, particularly the cytokeratin 5/6 (CK5/6), as well as cytokeratins 14 and 17. These pathological basal cell type TNBCs have a typical histopathological appearance, most being poorly differentiated grade 3 carcinomas, with some or all of the following microscopic features: solid growth pattern, a prominent lympho-plasmacytic infiltrate and a medullary-like growth pattern. The tumour

cells are characteristically markedly pleomorphic with pleomorphic nuclei, prominent mitotic activity and well-marked cellular apoptosis. There is usually extensive geographic tumour necrosis, which can be associated with the exceptionally high proliferative rate of these tumours. Some exhibit prominent stromal fibrosis. Characteristically, these tumours have a 'pushing' rather than an infiltrative border. Most of these tumours show the BL molecular characteristics as described by Perou et al.,[2] and some may show squamous differentiation and even spindle cell morphology (metaplastic carcinomas). These last two histological variants have been regarded to be BL variants.

The *PAM50* gene expression assay classifies breast cancers into at least five groups, including luminal A, luminal B, *HER2* enriched, BL and normal breast-like and this classification can be recapitulated with surrogate immunohistochemical markers, including OR, PR, HER2, EGFR1, CK5/6 and Ki67.[3–5] More recent gene expression array analysis has identified six different groups of TNBC, including two BL (BL1 and BL2), an immune-modulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL) and a luminal androgen receptor subtype (LAR).[3] A further group termed unstable (UNS) has been recognised.[6] The BL1 and 2 subtypes typically have a higher expression of cell cycle genes, while M and MSL are enriched for epithelial–M transition, and growth factor pathways. LAR, by definition, demonstrates AR overexpression.[3] The study of Matsuda et al.[6] has confirmed the work of Lehman.[3]

It is important, therefore, to note that while there is overlap between TNBC and BLBC, these two entities are not synonymous with one another and so the BL carcinoma is best regarded as a subset of TNBC. It has been demonstrated that only 71 % of TNBC are of BL subtype by gene expression profiling, and that only 77 % of molecular BLBC are triple negative.[7] Up to 70 % of patients with *BRCA1* mutations develop tumours that are morphologically identical to the BLBC and are often triple negative. These probably form a further subset of the basal-type carcinomas, but not all BRCA1-associated tumours are TNBC.

A recent study comparing BL TNBC assessed the three different modalities for defining TNBC, namely morphology, immunohistochemistry (IHC) and transcriptional profiles. In this study by Gazinska et al.,[8] those TNBC that were positive for CK5/6 and/or EGFR were designated as core basal, those with pathological criteria were designated as path-basal, and those designated according to molecular profiling (PAM50) were designated as PAM50 BL.[9] The non-core BL carcinomas may also be designated as 5-marker negative panel (5NP). In this study, only 13/116 (11 %) were defined as BL by all three modalities: it is evident that even the manner in which BL carcinomas are defined is problematic. The path–basal group had a significant decrease in nodal metastases, while the highest risk of death was in those immunohistochemically defined 'core–basal' TNBC. The path non-basal group included carcinomas that could only be designated as not otherwise specified (NOS). This latter group is associated with a higher risk of lymphovascular invasion and nodal metastases. BLBC, in contrast to normal breast basal or myoepithelial cells, expresses cytokeratins 8 and 18. This calls into question the initial implications of the microarray-based studies of breast cancers that suggest that BL cancers originate from basal myoepithelial cells. They may rather be derived from luminal progenitors.

Other types of tumour classified as TNBC include carcinomas morphologically designated as of no specific type (NST) – salivary gland-like carcinomas (particularly the adenoid cystic carcinomas and myoepithelial carcinomas), lobular and/or mixed features – while some papillary and secretory-like carcinomas may also be regarded as triple negative disease.

There are many lessons to be learned from all of the above data. First, TNBC is a group of several biologically different tumours. Second, IHC is necessary to define the core basal from the 5NP group. In the core basal group, the path non-basal will tend to act more aggressively than the path–basal group. Adenoid cystic and salivary-like carcinomas and secretory carcinomas have a favourable result. Recently identified subtypes may have a worse outcome, particularly the claudin-low subtype (with low expression of claudin genes).[5] Variants of this group, which exhibit stem cell features and a prominent CD8+ lymphocytic infiltrate, may also act aggressively.

Thus, the designation of TNBC as an entity is not sufficient and all efforts should be made to classify TNBC into subgroups further. This indicates that a further classification of TNBC would be appropriate, as would the identification of specific molecular abnormalities, particularly potential targets for chemotherapeutic agents.

Much work has been carried out in this respect and this has been well reviewed in a recent analysis of TNBC.[10] The BLBC, at the molecular level, show complex changes. Those associated with BRCA have been shown to harbour both mismatch repair defects and genomic instability.[11] Those in particular, which are p53-mutant, have responded best to high-dose alkylating agents. Repair of double-strand breaks requires a *BRCA1*/2-dependent process, resulting in homologous recombination, which repairs the break. The poly (adenosine diphosphate-ribose) polymerases (PARPs) regulate the base excision pathway and, thus, inhibition of PARP may lead to persistent double-stranded breaks, inducing cell death.

Currently, work is focused on varying kinase pathways, primarily those with phosphatase and tensin homologue (PTEN) losses and activation of the AKT pathway. This occurs in a third of TNBC.[12] Other significant molecular pathways include amplification of the fibroblast growth factor pathway (FGFR) 2, and vascular endothelial growth factor A (VEGFA), both of which are potential targets.[10] EGFR overexpression, which is intrinsic to the core basal variant of TNBC, may also be a potential target.

AR expression is found in a subset of TNBC. This pathway may represent an alternate mechanism by which OR-negative tumours regulate OR-dependent genes downstream. This also provides a potential target for blockade in this small subset of TNBC.[13]

Matsuda et al. described seven subtypes of both triple negative inflammatory breast cancer and triple negative non-inflammatory breast cancer. The authors found no association between TNBC subtype and inflammatory breast cancer status (p=0.47). TNBC subtype did not predict recurrence-free survival. The presence of inflammatory breast cancer phenotype was not a significant predictor of recurrence-free or overall survival (OS) in the TNBC cohort.[6]

The Role of Neoadjuvant Chemotherapy in the Treatment of Triple Negative Breast Cancer

Cytotoxic Chemotherapy

Neoadjuvant chemotherapy studies have reported higher response rates in TNBC than non-TNBC. The pathological complete response (pCR) has been shown to predict improved long-term outcomes for TNBC.[14,15]

Conventional cytotoxic chemotherapy and DNA-damaging agents continue to be the mainstay for treatment of this disease. Taxanes and anthracyclines are active agents in the management of TNBC and remain important agents, but have not shown specific benefit over non-TNBC. Platinum agents were initially tested in patients with advanced disease as a single agent and in combination with other drugs, and were shown to be active when given early during the disease.

Several studies have now demonstrated that TNBC has significantly higher pCR rates compared with hormone receptor positive breast cancer when treated with neoadjuvant chemotherapy, and that pCR correlates well with improved outcomes.

A large retrospective study from the MD Anderson Cancer Center compared the response to neoadjuvant therapy in TNBC to non-TNBC. In this study, patients with TNBC had significantly higher pCR rates (22 % versus 11 %; p=0.034) compared with non-TNBC, but the subset of TNBC not stratified for pCR had decreased 3-year progression-free survival (PFS) rates (p<0.0001) and 3-year OS rates (p<0.0001). TNBC was associated with increased risk of visceral metastases (p=0.0005), lower risk of bone recurrence (p=0.027), and shorter post-recurrence survival (p<0.0001). Recurrence and death rates were higher for TNBC only in the first 3 years. If pCR was achieved, patients with TNBC and non-TNBC had similar survival rates (94 % and 98 %; p=0.24). Patients with residual disease following neoadjuvant chemotherapy had worse 3-year OS if they had TNBC compared with non-TNBC (68 % versus 88 %; p=0.0001). These data confirmed the poorer prognosis in TNBC. The authors concluded that patients with TNBC have increased pCR rates compared with non-TNBC, and those with pCR have excellent survival rates. On the other side of the spectrum, patients with residual disease following neoadjuvant chemotherapy have significantly worse survival rates if they have TNBC compared with non-TNBC particularly in the first 3 years.[16]

This is confirmed by another retrospective study conducted in 435 patients between 1985 and 2003 in patients treated with neoadjuvant therapy for breast cancer. The OR-negative tumours were more likely to achieve a pCR than OR positive (21.6 % versus 8.1 %).[15] OS at 5 years was significantly higher in the OR-negative subgroup, which achieved a pCR (TNBC 90 % versus non-TNBC 52 %) in agreement with previous observations.[17]

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial randomised 2,411 women to one of three treatment arms to evaluate the response to neoadjuvant therapy and long-term results. Patients received either four cycles of standard adriamycin cyclophosphamide (AC) three times weekly versus four cycles of AC, followed by four cycles of docetaxel and subsequent surgery, or four cycles of AC followed by surgery and then four cycles of adjuvant docetaxel. The addition of preoperative docetaxel almost doubled the pCR rate from 12.9 % and 14.4 % in each of the two AC arms, to 26.1 % in the AC-D arm. Determination of hormone receptor status was not required for study entry. Subgroup analysis showed that the pCR rate practically doubled with the addition of docetaxel for both the OR-positive and OR-negative tumours from 5.7 % to 14.1 % and 13.6 % to 22.8 %, respectively. The pCR rate of the OR-negative subset itself was nearly double that of the OR-positive subset in each treatment group (5.7 % versus 13.6 % for AC and 14.1 % versus 22.8 % for AC-docetaxel). Again, patients who achieved a pCR had significantly better disease-free survival (DFS) and OS outcomes compared with patients who did not.[18,19]

The GeparDuo trial also evaluated the pCR rate in 913 women randomised to receive preoperative doxorubicin and docetaxel for four cycles or AC for four cycles, followed by docetaxel for four cycles (AD). The overall pCR rate was 10.6 % in the entire study population. There was an improvement from 7.0 % for patients treated with AD to 14.3 % with the three-drug regimen. In this study, the OR-negative subgroup was three times more likely to achieve a pCR compared with the OR-positive subgroup (22.8 % versus 6.2 %). A recent analysis of samples examined *HER2* positivity from the GeparDuo trial and confirmed that the triple negative subgroup had significantly higher pCR than the hormone receptor positive subgroup. Triple negative tumours could be divided into subgroups with different pCR rates according to their Ki-67 proliferation rate. Responses were more likely if the Ki-67 level was greater than 20 % (63.6 % versus 0 %; p<0.0001).[20]

Recently, there has been renewed interest in platinum compounds for the treatment of TNBC due to additional preclinical data that suggested platinum agents may be particularly active in TNBC and *BRCA1* associated breast cancer. Breast tumours arising in *BRCA1* mutation carriers share features with the BL tumours.[21,22] Nearly all *BRCA1* tumours are BL, but not all BL tumours have BRCA1 mutations. A high pCR rate of 65 % was seen in a single arm study of 74 patients with TNBC treated with cisplatin 30 mg/m^2, epirubicin 50 mg/m^2 and paclitaxel 120 mg/m^2 weekly for 8 weeks with granulocyte colony-stimulating factor (G-CSF) support on days 3 to 5. On this trial, patients who attained a pCR had 3- and 5-year DFS rates of 97 % and 90 %, respectively, compared with 3- and 5-year DFS rates of 61 % and 56 %, respectively, in those with residual disease after neoadjuvant chemotherapy. There were equal numbers of patients with T2 and T3 tumours. The pCR rate was significantly higher in the T2 tumours (74 % versus 51 %).[21–23]

Targeted Therapy

Anti-angiogenesis agents, such as bevacizumab, and treatment with PARP inhibitors have led to conflicting results.[24–26]

Anti-angiogenesis therapy was evaluated in TNBC in the GeparQuinto (GBG 44) study. This trial assessed the pCR rate after neoadjuvant epirubicin, cyclophosphamide and docetaxel containing chemotherapy with and without bevacizumab in patients with TNBC. The study included patients with untreated T1c-4d TNBC and represented a stratified subset of the 1,948 participants of the *HER2* negative part of the GBG 44 trial. Randomised patients received four cycles of epirubicin at 90mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks, followed by four cycles of docetaxel at 100 mg/m^2 every 3 weeks, each with or without bevacizumab at 15 mg/kg every 3 weeks, added to backbone chemotherapy treatment. A total of 340 TNBC patients were randomised to chemotherapy without and 323 with bevacizumab, respectively. The primary endpoint was pCR. The rate of pCR was 27.9 % without and 39.3 % with bevacizumab (p=0.003). Bevacizumab treatment was confirmed as an independent predictor of higher pCR in multivariate logistic regression analysis. The German group concluded that the addition of bevacizumab significantly increases pCR rates compared with chemotherapy without bevacizumab in TNBC.[27]

These findings were not confirmed in the NSABP B-40 neoadjuvant trial of 1,206 patients.[28] Women were randomly assigned to receive neoadjuvant chemotherapy consisting of docetaxel 100 mg/m^2 on day 1, or docetaxel 75 mg/m^2 plus capecitabine 825 mg/m^2 twice a day on days 1 to 14 or docetaxel 75 mg/m^2 on day 1, plus gemcitabine 1,000 mg/m^2 on days 1 and 8 for a total of four cycles. All regimens were followed by

treatment with AC at standard doses for four cycles. Patients were also randomly assigned to receive or not to receive bevacizumab at a dose of 15 mg/kg of body weight for the first six cycles of chemotherapy. Although there was a numerically higher pCR rate in patients with TNBC that received bevacizumab, this was not clinically significant. In contrast to the previous study when the rate of pCR was examined according to hormone-receptor status, the effect of bevacizumab was more pronounced in the hormone receptor positive subset (15.1 % without bevacizumab versus 23.2 % with bevacizumab; p=0.007), with a weaker effect in the hormone receptor-negative subset (47.1 % without bevacizumab versus 51.5 % with bevacizumab; p=0.34). Bevacizumab plus chemotherapy led to an increase in toxicity in both clinical trials, particularly hypertension, cardiac dysfunction and mucositis.

A subsequent analysis of the GBG 44 trial by the same German group prospectively validated that an increased lymphocytic infiltrate in breast tumour tissue is predictive for a response to anthracycline and taxane-based neoadjuvant chemotherapy, and is associated with a significant improvement in pCR rates.[29]

Additional ongoing trials in the neoadjuvant TNBC setting will further the knowledge in this field. The GeparSixto study is researching the addition of carboplatin to neoadjuvant therapy for patients with early-stage TNBC, as well as *HER2*-positive disease. A recent presentation at the American Society of Clinical Oncology (ASCO) meeting showed that the addition of carboplatin resulted in an improvement in pCR rate from 37.9 % to 58.7 % (p<0.05).[30]

The Cancer and Leukemia Group B (CALGB) 40603 are also evaluating the addition of carboplatin and/or bevacizumab to standard chemotherapy in the neoadjuvant setting for TNBC. They randomly assigned patients with newly diagnosed TNBC to chemotherapy, with or without bevacizumab, and included mandatory tumour biopsies and germ-line DNA. The study aimed to determine if the addition of carboplatin, bevacizumab or both to standard neoadjuvant chemotherapy significantly increased pCR rates in 454 patients with stage II/III TNBC. Patients with stage II/III TNBC were randomised in a two by two schema to receive weekly paclitaxel for 12 courses, plus dose-dense anthracycline/cyclophosphamide alone or with bevacizumab every 2 weeks for nine cycles, carboplatin area under the concentration-time curve (AUC) 6 every 3 weeks for four cycles, or the combination. The primary endpoint was pCR in the breast, and a secondary endpoint was pCR in the breast and axilla. The study was not powered to detect a difference in recurrence-free survival or OS. Importantly, the investigators evaluated the effect of carboplatin on all patients receiving it alone, or in combination, and the same for bevacizumab. The addition of carboplatin to standard neoadjuvant chemotherapy significantly increased the pCR in the breast and also in the breast plus axilla.

The pCR rates in the breast were 60 % for patients receiving carboplatin compared with 46 % in the non-carboplatin group, an increase of 76 % (p=0.0018). Defined by no disease in the breast or axilla, the pCR rates increased to 54 % and 41 %, respectively, a 71 % increase (p=0.0029).

The addition of bevacizumab was also associated with an improvement in pCR in the breast only (not the axilla), producing pCR in 59 % of patients receiving the drug and 48 % of patients not taking bevacizumab, a 58 % increase (p=0.0089). The pCR rates for both breast and axilla were 52 % and 44 %, respectively, a 36 % non-significant increase (p=0.0570).[31]

Adjuvant Chemotherapy for Triple Negative Breast Cancer

Cytotoxic Chemotherapy

Conventional chemotherapy remains the backbone of adjuvant systemic treatment for most patients with early TNBC. At present, comparisons between adjuvant chemotherapy regimens are retrospective in nature, therefore, the best drugs or drug combinations have not been established in prospective randomised trials for patients with early TNBC. Classic CMF (cyclophosphamide, methotrexate and 5-fluorouracil) has shown effectiveness, whereas limited data on the role of anthracyclines are available.[32,33] A meta-analysis shows that adjuvant docetaxel-based chemotherapy, compared with regimens without taxanes, is associated with an improvement in DFS and OS in TNBC.[34] Two studies demonstrated the superiority of docetaxel, doxorubicin and cyclophosphamide (TAC) in the triple negative phenotype over fluorouracil, doxorubicin and cyclophosphamide (FAC). The GEICAM 9805 study showed that TAC is more effective than in the adjuvant treatment of high-risk node-negative breast cancer. In the TNBC subset, the HR for DFS was 0.59 (95 % confidence interval [CI] 0.32–1.07; p=0.08) favouring TAC over FAC.[35] Similarly, the Breast Cancer International Research Group (BCIRG) 001 study also demonstrated TAC to be more effective than FAC in the adjuvant treatment of node-positive TNBC.[36] Subgroup analyses addressing 3-year DFS showed a non-significant trend (p=0.051) in the TNBC subgroup in favour of TAC over FAC (74 % versus 60 %, respectively; HR 0.50; 95 % CI 0.29–1.00). Inhibitors of DNA repair or specific tyrosine kinases have not yet been addressed in the adjuvant setting. In the absence of data from prospective trials that focus on adjuvant treatment of early TNBC, taxanes and an anthracycline-containing regimen or classic CMF may be considered reasonable choices. Conventional chemotherapy remains the basis of TNBC treatment according to the majority of national and international guidelines including National Comprehensive Cancer Network (NCCN),[37] St Gallen[38] and European Society of Molecular Oncology (ESMO).[39]

Targeted Therapy

Adjuvant bevacizumab was investigated in patients with TNBC in the open-label, randomised adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE) phase III trial. The investigators recruited patients with centrally confirmed triple negative operable primary invasive breast cancer from 360 sites in 37 countries. Patients were stratified by nodal status, chemotherapy (anthracycline, taxane or both), hormone receptor status (negative versus low) and type of surgery. Patients received a minimum of four cycles of chemotherapy either alone or with bevacizumab (equivalent of 5 mg/kg every week for 1 year). The primary endpoint was invasive DFS (IDFS). There were 1,290 patients who received chemotherapy alone and 1,301 who received bevacizumab, plus chemotherapy. At the time of analysis of IDFS, median follow-up was 31.5 months in the chemotherapy-alone group and 32.0 months in the bevacizumab group. After 200 deaths, no difference in OS was noted between the groups (HR 0.84, 95 % CI 0.64–1.12; p=0.23). Addition of bevacizumab versus chemotherapy alone was associated with increased incidences of grade 3 or worse hypertension in 154 patients (12 %) versus eight patients (1 %), severe cardiac events occurring at any point during the 18-month safety reporting period in 19 patients (1 %) versus two (<0.5 %), and treatment discontinuation of bevacizumab, chemotherapy, or both in 256 (20 %) versus 30 (2 %). The authors concluded that bevacizumab could not be recommended as adjuvant treatment in patients with TNBC.[40]

Future trials should compare standard adjuvant regimens with regimens that integrate a targeted agent, with platinum salts in the appropriate patient population.

Treatment For Metastatic Disease

Cytotoxic Chemotherapy

In the setting of metastatic breast cancer (MBC), the subtype of TNBC is relatively high and accounts for a larger number of breast cancer deaths due to its highly aggressive nature.[41–43] In essence, there is no protocol for the first-line metastatic treatment in previously treated TNBC patients who have subsequently presented with metastatic disease. For those patients presenting with metastatic disease, anthracycline-based chemotherapy, with or without a taxane, would be an appropriate first-line approach. The use of multidrug regimens in the treatment of patients with MBC is controversial. The 2009 European School of Oncology Metastatic Breast Cancer Task Force (6th European Breast Cancer Conference) recommended sequential monotherapy for advanced breast cancer, and suggested that patient- and disease-related factors should be used to best identify patients who may benefit from combination treatment.[44] Other consensus groups have recommended the use of combination treatment in patients with extensive visceral disease.[45] Therefore, given the often-aggressive nature of TNBC in the setting of extensive visceral disease, the use of a combination of drugs, rather than a single agent, is most often advocated.

Only a single prospective phase III trial looked at re-challenging with an anthracycline. In the study, patients with advanced breast cancer previously treated with neoadjuvant or adjuvant anthracycline were randomly assigned to receive either docetaxel or pegylated liposomal doxorubicin (PLD), followed by docetaxel.[46] Treatment with PLD–docetaxel significantly improved time to progression (TTP) (median 10 versus seven months) and overall response rate (overall response rate [ORR] 35 % versus 26 %). The clinical significance of this re-challenge approach needs to be treated with reserve as the cumulative doses of non-pegylated anthracyclines need to be closely monitored due to the potential for cardiotoxicity and the PLD has a different pharmacology.

Platinum-based treatments have in recent years received more attention for the treatment of TNBC, especially where there is a link to germ-line mutations in the *BRCA1* gene. Approximately 10 % of TNBC tumours have *BRCA1* mutations (and 90 % of BRCA1-mutated tumours are TNBC).[47,48] In a retrospective study, a regimen of cisplatin and gemcitabine in combination improved the result for patients with TNBC patients, regardless of whether a *BRCA1* mutation was present or not, despite these patients still having an overall poor prognosis.[49]

BRCA was investigated in TNBC in patients. Isakoff et al. reported *BRCA1*/2 mutation carriers in 14.5 % and *BRCA1/2*-WT in 85.5 % of patients in a cohort of 76 TNBC undergoing platinum-based treatment. An exploratory subgroup analysis showed a higher response rate to single-agent platinum chemotherapy in *BRCA1/2* carriers (54.6 %) compared with *BRCA1/2* wild type patients (26.2 %). Additionally, 7 % were long-term survivors with durable responses without a correlation with *BRCA1/2* mutations.[50,51]

Newer agents in the treatment of metastatic TNBC have emerged. Some are already registered for use and others may in the future add benefit to the treatment of these patients.

Ixabepilone is an epothilone anti-microtubule agent. In an open-label phase III trial, ixabepilone plus capecitabine was compared with capecitabine alone in patients with anthracycline pretreated or resistant, and taxane-resistant, locally advanced or MBC . Patients treated with ixabepilone plus capecitabine had a 25 % reduction in estimated risk of progression (HR 0.75, 95 % CI 0.64–0.88) compared with those who received capecitabine only.[52] The ORR was also greater for the ixabepilone-treated group (35 % versus 14 %). A subset analysis of TNBC patients has reported statistically superior PFS for the combination arm (4.2 versus 1.7 months). However, no increase in OS was shown.[49] Ixabepilone-treated patients did have more grade 3 or 4 adverse events, especially neuropathy (21 % versus 0 %) and neutropenia (68 % versus 11 %), which may limit the drug's clinical use when the side-effect profile is weighed up against its benefit and the patients' quality of life in the setting of metastatic disease.[53]

Eribulin has been investigated and approved for advanced or MBC in patients who have progressed after prior anthracycline and taxane regimens where suitable. This was based on the global phase III Eribulin Monotherapy versus treatment of physician's choice in patients with metastatic Breast CancEr (EMBRACE) study assessing treatment of the physician's choice versus eribulin. This study showed a significant increase in OS for the eribulin arm (median OS 13 versus 11 months).[54] Of the patients enrolled, 19 % had TNBC, and eribulin was most effective in hormone receptor negative patients who had a 34 % decreased risk of death compared with the control arm.

Targeted Therapy

The anti-VEGF monoclonal antibody, bevacizumab, has shown benefit in some TNBC subgroups if combined with taxanes and other agents.[55–59] In a meta-analysis of three phase III trials of bevacizumab as first-line treatment in a pooled subset of 621 patients with TNBC, the median PFS was longer in patients treated with bevacizumab plus chemotherapy than in those treated with chemotherapy alone (8.1 versus 5.4 months), but no difference in OS was seen.[56] Similar results were seen in a subgroup analysis of the RIBBON-2 trial, which investigated various chemotherapies with and without bevacizumab as second-line treatment of MBC.[59] In patients with TNBC (n=159), PFS with bevacizumab was improved (median 6.0 versus 2.7 months; p=0.0006). Again, while a trend towards improved OS was seen (HR 0.624), it failed to reach statistical significance (p=0.0534).[56] This agent is no longer approved for use in MBC by the Food and Drug Administration (FDA). However, it is still approved by European Medicines Agency (EMA) for the treatment of MBC.[60]

The anti-VEGF receptor tyrosine kinase inhibitors sunitinib and sorafenib have some activity in breast cancer trials with a 15 % response rate with sunitinib in a phase II trial. As yet, these agents are not approved for use in MBC.[61,62]

Sunitinib is an oral, multitargeted tyrosine kinase inhibitor that inhibits VEGF receptor (VEGFR), platelet-derived growth factor receptor, stem cell factor receptor (KIT) and CSF-1 receptor. Sunitinib monotherapy was evaluated in a phase II (open-label, multicentre study), in patients with MBC. In this trial, 64 patients previously treated with an anthracycline and a taxane received sunitinib 50 mg daily in 6-week cycles (4 weeks on; then 2 weeks off treatment). Seven patients (11 %) achieved a partial response (PR) (median duration, 19 weeks). Median TTP and OS were 10 and 38 weeks, respectively. In this study, responses occurred in TNBC tumours as well as *HER2*-positive

disease, trastuzumab-treated patients. The authors concluded that sunitinib is active in patients with heavily pretreated MBC.[61]

In a subsequent study, sunitinib was investigated in a randomised, open-label phase II study comparing the efficacy of sunitinib monotherapy with chemotherapy in patients with previously treated advanced TNBC who relapsed after anthracycline and taxane-based chemotherapy. Patients were randomised to receive either sunitinib or the investigator's choice of standard of care (SOC) chemotherapy. PFS was the primary endpoint. Median PFS was 2.0 months with sunitinib compared with 2.7 months with SOC chemotherapy. Median OS was not prolonged with sunitinib (9.4 months) compared with chemotherapy (10.5 months). The objective response rate was 3 % with sunitinib and 7 % with SOC chemotherapy. In this study, sunitinib monotherapy did not improve efficacy compared with chemotherapy in patients with previously treated advanced TNBC.[63]

Sunitinib was also investigated in a randomised phase III trial of 442 patients comparing sunitinib plus capecitabine (2,000 mg/m^2) with single-agent capecitabine (2,500 mg/m^2) in patients with heavily pretreated metastatic disease who failed anthracyclines and taxanes. The primary endpoint was PFS. The median PFS was not significantly different between the treatment arms (5.5 months for the sunitinib plus capecitabine arm compared with 5.9 months for the capecitabine monotherapy arm). There were no significant differences in response rate or OS. The addition of sunitinib to capecitabine does not improve the clinical result of patients with MBC pretreated with anthracyclines and taxanes.[64]

Sorafenib is a multikinase inhibitor with antiangiogenic/antiproliferative activity. Sorafenib was investigated in a randomised, double-blind, placebo-controlled phase IIB trial evaluating sorafenib with capecitabine for locally advanced or metastatic *HER2*-negative breast cancer. Patients in the first- or second-line settings were included. Patients were randomly assigned to capecitabine 1,000 mg/m^2 orally twice a day for days 1 to 14 of every 21-day cycle with sorafenib 400 mg orally twice a day or placebo. The primary endpoint was PFS. A total of 229 patients were enrolled. The total number of TNBC patients included in this trial was unbalanced (sorafenib 17.4 % versus placebo 29 %). The addition of sorafenib to capecitabine resulted in a significant improvement in PFS compared with placebo (median 6.4 versus 4.1 months with a hazard ratio [HR] of 0.58; p=0.001) with sorafenib favoured across subgroups, including first- (HR 0.50) and second-line (HR, 0.65) treatment. There was no significant improvement for OS (median 22.2 versus 20.9 months, HR 0.86; p=0.42) and overall response (38 % versus 31 %; p=0.25). The main toxicities of any grade in the sorafenib arm compared with placebo included diarrhoea (58 % versus 30 %), rash (22 % versus 8 %), mucositis (33 % versus 21 %), neutropenia (13 % versus 4 %), hypertension (18 % versus 12 %) and hand–foot skin reaction/hand–foot syndrome (HFSR/HFS) (90 % versus 66 %). Grade 3 to 4 toxicities were similar between treatment arms except HFSR/HFS (44 % versus 14 %). The investigators concluded that the addition of sorafenib to capecitabine improved PFS in patients with *HER2*-negative advanced breast cancer. Subset analysis for TNBC patients was not reported. Additionally, the dose of sorafenib used in the trial resulted in unacceptable toxicity for many patients.[62] A phase III confirmatory trial has been completed with a reduced sorafenib dose. Results of this study will be available in the near future.[65]

PARP inhibitors showed promising activity in an early phase II study. The trial compared the efficacy and safety of gemcitabine and carboplatin, with or without iniparib, in patients with metastatic TNBC. A total of 123 patients were randomly assigned to receive gemcitabine at a dose of 1,000 mg per square meter and carboplatin at a dose equivalent to an AUC of 2 on days 1 and 8. Patients were randomised to receive iniparib at a dose of 5.6 mg per kilogram of body weight on days 1, 4, 8 and 11 every 21 days.[66]

Results showed that the addition of iniparib to gemcitabine and carboplatin improved the rate of clinical benefit from 34 % to 56 % (p=0.01) and the ORR from 32 % to 52 % (p=0.02). The median PFS improved from 3.6 months to 5.9 months (HR for progression 0.59; p=0.01) and the median OS from 7.7 months to 12.3 months (HR for death 0.57; p=0.01). These promising results were not replicated in a well-designed and powered phase III trial. The median OS was 11.1 months in the control arm compared with 11.8 months on the iniparib arm.[67]

EGFR is overexpressed in 60 % of BL cancers. The EGFR monoclonal antibody cetuximab was investigated in the Cetuximab and Cisplatin in the Treatment of "Triple Negative" (Estrogen Receptor [ER] Negative, Progesterone Receptor [PgR] Negative, and Human Epidermal Growth Factor Receptor 2 [*HER2*] Negative) Metastatic Breast Cancer (BALI-1) trial that looked at cetuximab in combination with cisplatin (n=173) for the treatment of metastatic TNBC versus cisplatin alone. An overall response rate of 20 % versus 10 % was seen, with a PFS of 3.7 versus 1.5 months.[68,69] As yet, the use of cetuximab is not registered for use in metastatic TNBC.

Cetuximab was also investigated in the Translational Breast Cancer Research Consortium (TBCRC) 001 study. In this randomised phase II trial, patients received cetuximab at a loading dose of 400 mg/m^2 followed by 250 mg/m^2 per week intravenously (IV) alone, with carboplatin (AUC of 2, once per week, IV added after progression, or as concomitant therapy from the beginning). A total of 102 patients with TNBC (74 % had BL molecular subtype) were included on this study. The response rate was 6 % (two out of 31) to cetuximab and 16 % (four out of 25) to cetuximab in combination with carboplatin after progression. Although the combination of cetuximab plus carboplatin regimen was well tolerated, TTP and OS were short at 2.1 and 10.4 months. The combination of cetuximab plus carboplatin produced responses in less than 20 % of patients in metastatic TNBC.[70]

Other targeted agents such as the mammalian target of rapamycin (mTOR) inhibitor everolimus and the anti-EGFR erlotinib were investigated in patients with MBC. These agents are associated with minimal activity in the clinical setting of metastatic TNBC.[71,72]

Hormonal Anti-androgen Treatment

Endocrine therapy is ineffective in breast cancer patients with hormone receptor-negative disease. However, in OR- and PR-negative disease there is a subset with the AR expression that is predictive to respond to anti-androgen therapies of 12 %. A phase II study explored bicalutamide in the subset of AR-positive metastatic disease. In this study, AR was tested by IHC and considered positive if the nuclear staining was greater than 10 %. Patients were treated with bicalutamide at a dose of 150 mg daily. The primary endpoint of this study was defined as the total number of patients who showed a CR, PR, or stable disease (SD) after 6 months. The percentage of patients showing clinical benefit (CR, PR and SD) was 19 % (95 % CI 7–39 %) for bicalutamide. The median PFS was 12 weeks (95 % CI 11–22 weeks). Bicalutamide was well tolerated with moderate activity in patients with OR- and PR-negative, AR-positive

breast cancer. Unfortunately, the role of anti-AR targeted drugs is limited. TNBC represents 20 % of the disease, and 10 % of that is AR positive, so only 2 % of overall breast cancer cases may benefit from this form of treatment.[73]

Conclusion

The heterogeneous TNBC group of patients will no doubt be better defined into subgroups in the future which will improve our understanding of the disease, allowing the use of newer targeted agents to further improve patient outcomes. Currently, the mainstay of treatment in the neoadjuvant, adjuvant and first-line metastatic setting remains the use of anthracycline, alkylating agents, anti-metabolites and taxane-based chemotherapy. The addition of carboplatin in the neoadjuvant treatment of TNBC improved pCR; the role of bevacizumab, however, is not established due to conflicting data. ■

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