Personalising the Fight against Triple Negative Breast Cancer

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Abstract

Triple Negative Breast Cancer (TNBC) is a highly heterogeneous disease. Lacking hormone receptors, ER and PR, as well as HER2 amplification, these cancers cannot be treated with more modern, targeted therapies such as tamoxifen or trastuzumab. Thus, the current standard of care for these patients is cytotoxic chemotherapy with varied clinical response. However, all patients experience unwanted and debilitating side effects regardless of response. Therefore, TNBC represents a significant unmet clinical need and finding more targeted and effective treatment approaches for this aggressive disease is an area of active research. The success of such agents has been hindered by the heterogeneity of the disease, with many new drugs only showing promising results in small populations. In order for targeted treatments to succeed, predictive biomarkers must be developed which can stratify patients and drive treatment choices. This review looks at the most promising areas of research regarding targeted therapy in TNBC as well as associated biomarkers that can be used to guide treatment.

Keywords: Triple negative breast cancer; Biomarkers; Personalised medicine; Targeted treatment

Introduction

The term triple negative breast cancer (TNBC) is used to describe a subset of breast cancers that are Estrogen Receptor (ER) negative, Progesterone Receptor (PR) negative and lack amplification of the Human Epidermal growth factor Receptor 2 (HER2) gene. Despite accounting for only approximately 15% of all breast cancers, TNBC accounts for a disproportionately high rate of mortality overall [1]. This is due to the aggressive and invasive nature of TNBC coupled with the lack of unique molecular targets available for directed therapy. Examples of such targeted treatments include anti-estrogens such as tamoxifen and anti-HER2 therapies such as trastuzumab (Herceptin®), which are used to treat ER- and HER2-positive breast cancer respectively [2]. Compared to other subtypes of breast cancer, TNBC has a propensity to disseminate to visceral organs such as the lungs or brain rather than bone [3]. Tumours are typically larger and more frequently lymph node positive [3,4], all of which indicates a unique biology. Rates of TNBC are higher in African American and Hispanic women and TNBC tends to occur in younger women [3,5]. Cancers arising from mutations in the breast and ovarian cancer tumour suppressor gene, BRCA1, also tend to be triple negative. Interestingly, a subset of sporadic TNBCs with wild type BRCA1 share features associated with BRCA1 dysfunction, such as genomic instability and faults in DNA repair mechanisms. This phenomenon is known as "BRCAness" [6]. This indicates a potential role for BRCA1 in both sporadic and hereditary TNBCs, and therapies targeting the BRCA1 pathway could have applications in sporadic TNBCs.

TNBC heterogeneity

TNBC is a diagnosis of exclusion defined by the lack of the ER, PR and HER2 biomarkers and this results in a high degree of heterogeneity. Given the poor outcome associated with TNBC as a whole, further stratification and tailored treatment options are required in order to improve the management of these patients.

Numerous studies have further sub-classified TNBC using varied techniques such as immunohistochemistry (IHC) and 'omic' strategies [7,8]. A number of clinically validated classification methods that were developed for breast cancer as a whole have been studied in the context of TNBC specifically. Application of the PAM50 classifier (an intrinsic gene signature shown to classify tumours with clinically relevant subgroups) revealed that the majority (80%) of TNBCs are basal-like. The remaining tumours are classified as HER2 enriched (10.2%), normal-like (4.6%), luminal B (3.5%) and luminal A (1.1%) [9]. Conversely, most, but not all, basal-like breast cancers (BLBC) are triple negative in nature [10] with up to 26% of these cancers being ER/PR positive or displaying amplification of HER2 [9,11]. Application of the integrative clusters (IntClust) classifier (defined by a combination of copy number and gene expression data revealing 10 clusters of breast cancer), showed that BLBC contains a

heterogeneous distribution of these clusters, with IntClust 4 and 10 representing over 80% [12]. IntClust 10 is defined by a high degree of genomic instability and chromosomal aberrations. Conversely, IntClust 4 is associated with a lack of copy-number variation, high immune infiltrate and an overall favourable outcome [13]. BLBC and TNBC are not synonymous but given the strong degree of overlap, the integrative clusters present in TNBC can be inferred from the analysis of basal-like tumours.

Further studies have developed TNBC specific classification methods. Lehmann BD, et al. [8,14] proposed 6 possible subgroups for TNBC based on Gene Expression (GE) profiles which was then further refined into 4 subgroups in a validation study (herein referred to as the Vanderbilt subtypes). These 4 subgroups consist of two basal-like subgroups (BL1, BL2), a Mesenchymal (M) and a Luminal Androgen Receptor subgroup (LAR). The gene signatures that identified the two previously included subgroups (immunomodulatory and mesenchymal stem-like) were determined to be from infiltrating lymphocytes and/or stromal cells rather than the tumour epithelial cells [8]. Apart from having distinct gene expression patterns, these subgroups displayed a range of clinical and histological differences (grade, stage and metastases) [8]. Furthermore, these subgroups do not respond uniformly to chemotherapy. The BL1 subgroup is associated with elevated cell cycle and DNA damage response gene expression and exhibited the highest response rates to chemotherapy (anthracycline/cyclophosphamide/taxane based). Pathologic Complete Response (pCR-lack of residual disease in the breast and axillary lymph nodes after treatment) rates for this subgroup were 53%; higher than any other subgroup. The BL2 subgroup had characteristic growth factor signalling and myoepithelial markers. This subgroup had the poorest response to treatment, with a 0% pCR rate. The M subgroup, with a pCR rate of 31%, displayed elevated levels of genes responsible for epithelial-mesenchymal transition and growth factor signalling, with enrichment in pathways involved in cell motility and differentiation. The LAR subgroup was defined by high levels of androgen receptor gene signalling and luminal cytokeratin expression. The LAR subtype cancers responded poorly to chemotherapy with pCR rates of just 10% [15,16].

Other groups have attempted to classify TNBC into clinically relevant subtypes, however these analyses have not been validated and characterised to the same extent as the Vanderbilt subtypes. Burstein MD et al. [7] subtyped TNBC *via* DNA/RNA profiling. They identified four TNBC subtypes: LAR, Mesenchymal (MES), Basal-Like Immune Activated (BLIA) and Basal-Like Immune Suppressed (BLIS). Each subtype varied with respect to treatment targets and prognoses. A further study using gene expression to subtype TNBC divided tumours into three clusters: C1-LAR, C2-basal like with low immune response/high M2-like macrophages (BLLIR), C3-basal like with high immune response/low M2-like macrophages (BLHIR) [17].

It is apparent that appropriate subtyping is the critical first step in order to identify biomarkers that can stratify patients in order to optimise treatment choices (Table 1). There appears to be a general trend among most studies of two basal-like subtypes, an androgen receptor expressing subtype, and a subtype associated with immune signalling. The reaching of a consensus on this issue will aid the identification of trends in this heterogeneous population and allow a more personalised approach to be used, ultimately leading to improved patient outcome.

Treatment of TNBC

Despite the poor overall prognosis and lack of molecular targets for treatment, patients with TNBC tend to have an overall higher response to chemotherapy than other cancers. This is known as the "TNBC paradox" [12,18]. This TNBC phenomenon may be explained by the fact that following chemotherapy, approximately two thirds of patients have favourable response and, when studied in the neoadjuvant setting, achieve a pCR [1,3]. These patients are classified as "good responders". In contrast, the remaining patients ("poor responders"), present with cancers that are either intrinsically resistant to chemotherapy or rapidly develop resistance with residual disease post-treatment [3]. These patients have unfavourable outcomes and a high rate of recurrence. Typically, less than 30% of these patients will survive beyond 5 years [12,14]. This can be attributed to the aggressive nature of TNBC and the lack of therapeutic alternatives to chemotherapy when treatment fails.

There also appears to be a strong time-dependent link between failure of chemotherapy and progression/death. Liedtke C et al. [1] showed that there is a significantly higher risk of progression and death in TNBC in the first 3 years following diagnosis, after which the risk falls and is comparable, if not lower than that of non-TNBC. Such trends are in stark contrast to non-TNBC cases which show an unchanging risk of relapse over time [1]. This illustrates how overall survival of TNBC is intrinsically linked to the response to first line treatment, with good responses leading to long term survival.

The TNBC paradox has led to many trials attempting to ascertain the optimal chemotherapy regimen for TNBC. The current generally accepted Standard of Care (SoC) for TNBC is an adjuvant regimen of cytotoxic chemotherapy, often containing anthracyclines, with the addition of taxanes in response to lymph node involvement. However, following a number of clinical trials and reviews there is now a shift towards the use of neoadjuvant regimens consisting of an alkylating agent plus anthracycline and taxane based agents. This has been extensively reviewed elsewhere and now forms the basis of the American Society of Clinical Oncology (ASCO) guidelines for the treatment of TNBC [19-22]. In addition to the improved patient outcomes, neoadjuvant treatment also allows clinicians to measure and assess response to chemotherapy more readily as tissue is available for analysis following resection [19,21]. Furthermore, this may be a suitable treatment strategy for patients who present with tumours that are inoperable. In addition to changes in the timing of treatment, the frequency/density of chemotherapy is also under investigation. Some studies have shown that the use of dose dense regimens of adjuvant chemotherapy in TNBC lead to improvements in Disease Free Survival (DFS) and Overall Survival (OS) [23,24].

While anthracyclines and taxanes have formed the backbone of chemotherapy to date, other agents have been investigated with promising results. These include platinum agents (discussed below) as well as capecitabine which was investigated in the CREATE-X trial for patients with HER2 negative disease displaying residual disease following neoadjuvant chemotherapy. The addition of capecitabine to SoC in these patients prolonged DFS and OS [25]. This may represent a treatment option for this poor outcome population.

In order to improve survival in TNBC as a whole, we must develop biomarkers to stratify patients and tailor treatment options accordingly. It would appear that the subset of TNBC patients who respond well to the current standard of chemotherapy should continue to receive such therapy. However, there is a dearth of alternative treatment options for the patients who do not respond. Several agents are under investigation in the clinical and pre-clinical setting with different targets and biomarkers designed to augment treatment (Table 2). This review is designed to interrogate emerging treatment strategies and biomarkers in TNBC in tandem with landmark clinical trials.

Table 1: Subtyping studies on patient biopsies diagnosed with TNBC

Reference	Cohort	Method used	Subtypes	Comments
Lehmann [8, 14]	N=587	Gene expression	BL1, BL2, M, LAR (Formerly IM & MSL)	BL1 highest pCR rates & genomically unstable, BL2 lowest pCR rates
Burstein [7]	N=84 (validated in 114)	RNA/DNA Profiling	LAR, MES, BLIA, BLIS	BLIS worst prognosis, BLIA best prognosis
Jézéquel [17]	N=107 (validated in N=87)	Gene expression	C1-LAR, C2-BLLIR, C3-BLHIR	C3 tumours have best outcome
Curtis [13]	N=997 (discovery), N=995 (validation)	Gene expression/copy number analysis	IntClust 1-10	Clusters with distinct clinical outcomes, intrinsic subtypes split between clusters
Lehmann [10,105]	N=374	Gene expression signature (PAM50)	Basal-like, HER2, Normal-like, Luminal A, Luminal B	80% TNBCs basal-like when PAM50 classifier is applied

Table 2: Summary of emerging treatment targets in TNBC along with associated drugs and biomarkers

Drug Class/Target	Example Drug (s)	Associated Biomarker (s)
PARP	Olaparib	BRCA1/HRD
Platinum agents	Cisplatin/Carboplatin	HRD
AR	Enzalutamide	AR expression/LAR type TNBC
EGFR	Cetuximab	EGFR expression
VEGF	Sunitinib	VEGF1/2 expression
Tyrosine Kinase Inhibitors	Dasatinib/Bosutinib	C-kit, Src
PI3K/mTOR	Everolimus/Temsirolimus	LAR type TNBC
Immunotherapy	Avelumab	PL-L1/PD1, TIL
CDK4/6	Ribociclib/Palbociclib	LAR type TNBC

PARP Inhibition

Poly (ADP-ribose) Polymerase (PARP) 1 is a nuclear enzyme that is involved in a number of cellular pathways leading to DNA repair and apoptosis. PARP catalyses the transfer of ADP-ribose to target proteins which activates the signalling mechanisms necessary for cell survival and is responsible for the repair of single strand breaks by Base Excision Repair (BER) [12]. Inhibition of PARP leads to the accumulation of single strand breaks that degenerate into double strand breaks in replicating cells [26]. Such breaks can be repaired through Homologous Recombination (HR). However, in cells that are deficient for BRCA1 and BRCA2, HR is impaired which results in an accumulation of unrepaired DNA damage and apoptosis ensues. This concept is known as synthetic lethality, meaning that inhibition of PARP will only lead to toxicity in cells which have impaired HR (i.e. tumour cells), while normal cells will be able to repair the DNA damage and survive [27,28].

PARP inhibitors, recently approved for the treatment of BRCA mutated breast and ovarian cancer [29,30], may also have a role to play in the treatment of TNBC given their association with BRCAness. As these tumours are thought to display Homologous Recombination Defects (HRD), they are predicted to be more susceptible to DNA damaging agents such as PARP inhibitors. In addition, inhibition of PARP upregulates cellular sensitivity to chemotherapy and ionising radiation [12,27].

Clinical trials have been conducted to investigate the safety and efficacy of PARP inhibitors in TNBC, both as monotherapy and in combination with other agents. Olaparib, an orally available PARP inhibitor has been implemented in BRCA associated breast cancer at high (400 mg twice daily) and low (100 mg twice daily) doses in the ICEBERG 1 trial (Including 29 TNBC patients out of the 51 BRCA mutated cancers) with response rates ranging from 22% to 41% and minimal toxicity [31]. The OlympiAD trial, a recent phase III clinical trial, assessed the use of olaparib as monotherapy *versus*

SoC for BRCA mutated, HER2 negative Metastatic Breast Cancer (MBC) [32]. The primary endpoint for this trial was Progression Free Survival (PFS). 302 patients were recruited and assigned to receive either olaparib 300 mg twice daily (N=205) or standard care of the physician's choice (N=97). The olaparib group had improved PFS (7 months *vs* 4.2 months) and response rates (59.9% *vs* 28.8%). Olaparib monotherapy also led to reduced adverse events compared to standard care (eribulin, capecitabine, vinorelbine). The authors concluded that olaparib monotherapy was an effective treatment strategy for these patients. Olaparib has also been investigated in combination with weekly paclitaxel in patients with metastatic TNBC. Although some response was observed, this was associated with adverse effects such as neutropenia, diarrhoea and nausea [33]. Other studies have failed to show significant response rates to olaparib as a single agent in TNBC [34], suggesting more trials are needed in the TNBC setting to determine whether efficacy in BRCA mutated cancers can be translated to TNBC. Another PARP inhibitor, iniparib showed increased response rates, clinical benefit and PFS in a phase II trial, when used in combination with gemcitabine and carboplatin compared with gemcitabine and carboplatin alone [35]. This study however, failed to progress past phase III trials as the primary endpoints of clinical benefit and rate of stable disease were not met [36]. Studies involving iniparib have since been discontinued as it has failed to demonstrate adequate inhibition of PARP in *in vitro* studies [37]. Iniparib was shown to act through modulation of reactive oxygen species, rather than being a true PARP inhibitor and exhibited 1000-fold less activity than other PARP inhibitors [38]. Activity in previous clinical trials was attributed to non-selective interactions with various proteins. Other trials involving PARP inhibitors are ongoing and there are several new agents in clinical trials such as veliparib and talazoparib, estimated to be completed in 2019. [12,39]. EMBRACA is an ongoing clinical trial looking at talazoparib for the treatment of advanced breast cancer with a germline BRCA mutation [40]. Initial results suggest that talazoparib as monotherapy is potentially more effective than standard

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of care chemotherapy. The phase III trial BrighTNess has found that the addition of carboplatin to SoC neoadjuvant chemotherapy in TNBC improved pCR rates, however the addition of veliparib and carboplatin in combination added to toxicity with no improvement in efficacy [41]. Heterogeneity may account for the differing success rates of clinical trials involving PARP inhibitors. In an unstratified TNBC population, where only BRCAness patients are predicted to respond, sufficient numbers displaying this phenotype may not be present and this will inevitably lead to failure of clinical trials. Further trials that divide TNBC into sub-groups before treatment are critical to future successful clinical testing of these therapies.

This highlights the need for a biomarker for BRCAness. A number of assays are being developed/tested with this goal in mind. The BRAC Analysis® assay (Myriad Genetics Inc, Salt Lake City, USA) is an FDA approved test for BRCA 1/2 mutations in patient blood, used to inform choice for use of PARP inhibitors [42]. It detects variants in the protein coding regions of BRCA 1/2 genes and is used as a companion diagnostic alongside Lynparza® (Olaparib). Another assay currently in development from Myriad Genetics is the MyChoice® HRD assay, which is a DNA based assay that assigns a score based on tumour loss of heterozygosity, telomeric allelic imbalance and large scale state transitions [43]. Other approaches to this end include analysing gene expression signatures to assess BRCAness. One group has demonstrated that the use of a novel gene expression signature algorithm is more predictive of PARP inhibitor response than assessment of BRCA1/2 status in cancer cell lines. This algorithm identified patients with DNA repair deficiencies without BRCA1/2 mutations as well as those with mutations in BRCA1/2 that were resistant to PARP inhibition [44]. Such *in vitro* studies need to be clinically tested/validated before being used as treatment guides. Additionally, the DNA Damage Response Deficiency (DDRD) assay has been shown to be a statistically significant predictor of response to DNA damaging chemotherapy [45]. This gene microarray-based assay consisting of a 44 gene signature detects abnormalities in the Fanconi anaemia/BRCA/DDR pathway and has since been shown to be driven at a molecular level by the cGAS/STING pathway [46]. In one cohort studied, 32.5% of patients successfully predicted to achieve a pCR were BRCA1/2 wild type, demonstrating the DDRD assays ability to detect faults in DNA damage repair unrelated to BRCA1/2 mutations [45]. The assays described have been proven to be useful tools guiding PARP inhibitor treatment in *in vitro* and/or retrospective analyses. The application of these assays in clinical trials and in routine practice could improve outcomes for patients who would otherwise go undetected, receiving ineffective treatments.

Platinum Agents

Carboplatin and cisplatin are bi-functional alkylating agents that intercalate in the DNA causing inter- and intra-strand breaks. TNBC represents a group of cancers that are predicted to be sensitive to such agents [47].

Silver DP, et al. [48] found that 22% of patients with TNBC, including both wild type and mutant BRCA1, treated with single agent cisplatin achieved a pCR, with 64% showing either a complete or partial response. The CALGB40603 trial demonstrated the addition of carboplatin to neoadjuvant chemotherapy increased pCR rates from 44% to 60% among 443 patients with stage II/III TNBC [49]. These results are promising but must be interpreted with caution as the addition of platinum agents in the adjuvant setting has not significantly impacted Relapse Free Survival (RFS) or OS in studies to date [50,51]. This may be due to the fact that such trials are carried out on unstratified TNBC populations with wide genetic and clinical heterogeneity.

Significant end points cannot be reached unless the relevant treatment groups likely to benefit from treatment are identified and selected for during clinical studies. This has been demonstrated in the TNT trial which compared carboplatin *vs* docetaxel in TNBC, while taking into account BRCA1/2 status [52]. Patients with BRCA1/2 mutations treated with carboplatin had twice the Overall Response Rate (ORR) of those treated with docetaxel (33% *vs.* 68% respectively). In the unselected population, there was no significant difference between the two therapies, which demonstrates how selecting for a BRCAness population can increase the efficacy of platinum agents significantly. A systematic review of the use of platinum agents in TNBC by Poggio F, et al. [53] revealed that the addition of platinum agents to standard anthracycline/taxane based neoadjuvant chemotherapy significantly increased pCR rates in TNBC. Interestingly, they found that this effect was not limited to BRCA-mutated breast cancers, implying these agents could have clinical benefit for a larger proportion of TNBC patients.

The same biomarkers and assays used to measure BRCAness/DNA damage repair discussed previously could be applied in the context of platinum agents. As these drugs target cells with an inability to repair DNA, defects in the DNA damage response pathway or in homologous recombination could reveal tumours that are highly susceptible to them.

Androgen Receptor Targeting

Targeting of the Androgen Receptor (AR) has emerged as an intriguing approach to the treatment of TNBC. AR is a steroid hormone receptor responsible for sexual differentiation and reproductive development [54]. Binding of androgen to the receptor leads to translocation to the nucleus and activation of various transcription factors resulting in cellular proliferation and survival. A number of IHC-based studies have identified an AR positive subgroup of TNBC though the proportions vary based on antibodies and criteria used. For example, three different trials using a threshold of >10% nuclear expression found AR positive TNBC rates of 12%, 38% and 66% respectively [55-57]. The Luminal Androgen Receptor (LAR) molecular subtype of TNBC described by Lehmann BD, et al. [8,14] accounts for 11% of TNBC and has the unique feature of having growth driven by, and dependent on, androgen receptor signalling. Furthermore, the LAR subtype responds poorly to conventional chemotherapy compared to other subtypes, with one of the lowest pCR rates-just 10% [15]. Despite the LAR subtype showing highest expression of AR, it has also been shown that expression of AR is also present in non-LAR subtypes of TNBC highlighting the varied results found when different classification methods are applied to TNBC [58,59].

Following the success in prostate cancer, several investigations into the efficacy and safety of androgen receptor targeting in the treatment of TNBC have proceeded into early phase clinical trials. A phase II trial using bicalutamide, a non-steroidal, orally available competitive inhibitor [55] showed that AR was expressed in 12% of TNBCs (51 out of 424 patients) and the use of bicalutamide in these patients gave a Clinical Benefit Rate (CBR) of 19% and a median PFS of 12 weeks. CBR was defined as the percentage of patients who achieved a complete response, partial response or who had stable disease after 6 months. Bicalutamide was well tolerated with minimal adverse effects. This study also found that patients with AR positive TNBC tended to be older patients, with more soft tissue and bone metastases, which is atypical for TNBC [55].

Enzalutamide is another AR inhibitor that is currently approved in the treatment of prostate cancer. It acts by preventing the nuclear

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translocation of the receptor, thus inhibiting DNA binding activity [60]. A phase II clinical trial looking at the use of enzalutamide in AR positive TNBC has shown promising results [57]. This study showed CBR rates of 25% at 16 weeks and 20% at 24 weeks in 78 AR positive patients, selected for from 118 TNBC cases. There were also 2 complete responses and 5 partial responses. Enzalutamide was well tolerated in these patients, with only mild side effects reported such as nausea, fatigue and decreased appetite. Enzalutamide also increased OS (12.7 months to 17.6 months) and PFS (2.9 months to 3.3 months). Finally, a phase II, multi-centre clinical trial of abiraterone acetate, an orally available AR inhibitor, used in AR positive TNBC showed a 6 month CBR of 20% with one patient showing a complete response and 5 patients showing stable disease [56]. 53 out of 138 (38%) TNBC patients were deemed to be AR positive, 30 of whom were evaluable for the primary endpoint of 25% CBR. Although this endpoint was not reached, these results are clinically relevant as they show that this treatment approach has some activity in the selected patient group. These studies collectively indicate that a group of patients within the umbrella term of TNBC would benefit from the use of AR antagonists in their treatment [54,61,62].

In addition to improving treatment choices, the prognostic capabilities of AR could extend to predicting disease progression and response to current SoC treatment. One study examined novel prognostic biomarkers in TNBC and noted the positive association between AR and DFS/OS [63]. This study also showed that the absence of AR was associated with higher histological grade and greater likelihood of metastasis. It is clear that the role of AR in TNBC should not be disregarded and warrants further interrogation for use as both a prognostic and predictive biomarker.

EGFR Inhibition

The Epidermal Growth Factor Receptor (EGFR) is emerging as a novel druggable target and prognostic biomarker in TNBC. This receptor is involved in stimulating cellular proliferation through multiple downstream pathways such as MAPK and AKT, and inhibition can be used to reduce tumour growth. EGFR has been shown to be over expressed in TNBC/BLBC compared to other subtypes, holding potential for use as a target [2,64,65]. Inhibitors of EGFR have been developed and are currently approved for the treatment of various conditions. Cetuximab is a chimeric monoclonal antibody that binds to, and inhibits EGFR, which is currently used in the treatment of colorectal cancer [66]. The small molecule tyrosine kinase inhibitors erlotinib and gefitinib are also currently approved for the treatment of a range of cancers including lung and pancreatic [64].

The efforts to find new, more targeted approaches to the treatment of TNBC have led to several clinical trials involving EGFR inhibitors both as a monotherapy and in addition to cytotoxic chemotherapy. A phase II clinical trial (TBCRC 001) by Carey LA, et al. [67] examined the use of cetuximab alone, or in combination with carboplatin in stage IV TNBC. Response rates (the primary endpoint) of patients in this trial were modest, at 6% (2 of 31) for cetuximab alone and 16% in combination with cisplatin (4 of 25). This trial also failed to show a significant increase in PFS or OS. However, the combination of cisplatin and cetuximab *vs* cisplatin did double the ORR from 10% to 20% in the combination arm and there was no significant increase in toxicity. While the primary endpoints in this study were not met, the use of EGFR inhibitors as an add-on therapy to cytotoxic chemotherapy does appear to show some clinical benefit. Additional studies have shown promise in the addition of EGFR inhibitors to conventional chemotherapies such as irinotecan and carboplatin [68]. The N0436 study, a phase II clinical trial, demonstrated the combination of cetuximab and irinotecan in MBC showed improved clinical benefit in the TNBC subgroup *vs* non-TNBC (response rate 18% *vs* 0%) [69]. Erlotinib, a small molecule tyrosine kinase inhibitor that targets EGFR, was evaluated in combination with platinum/taxane based chemotherapy using 2 regimens, leading to pCR rates of 39% and 50% [70].

There can be no doubt that the selective treatment of patients with high EGFR levels may lead to improved response rates in clinical trials of EGFR-targeted agents. The expression of EGFR has also been shown to be associated with poor survival (log rank p=0.007), supporting its use as a prognostic biomarker [71]. EGFR expression has been shown to be associated with TNBCs that are more difficult to treat and correlates with significantly reduced 10-year survival rates [72]. Indeed, retrospective studies found that expression of EGFR leads to reduced DFS and OS in patients with TNBC [73,74]. A study in Japan has also revealed an increased EGFR copy number in TNBC compared to non-TNBC [75]. EGFR expression correlates with aggressive features (>3 lymph nodes, grade 3) [73] and patients expressing EGFR are unlikely to respond to chemotherapy [63]. These findings have the potential to impact current SoC for patients, and could facilitate a personalised approach to care, leading to treatment with optimal benefit.

VEGF Pathway Inhibition

TNBC is a highly proliferative cancer which relies on constant formation of new blood vessels for growth and survival. Therefore, the Vascular Endothelial Growth Factor (VEGF) pathway is important in the pathophysiology of TNBC. Signalling from the VEGF receptor is essential in the formation of new blood vessels (angiogenesis) as well as invasion of tumours and increased vascular permeability [76]. This increase in vascular density triggered by VEGF signalling gives rise to more aggressive tumours in breast cancer [77].

Monoclonal antibodies targeted against VEGF or tyrosine kinase inhibitors, which prevent phosphorylation associated with downstream signalling have been developed. Bevacizumab is a humanised monoclonal antibody that specifically binds to, and inhibits, VEGF-A and associated isoforms [26]. It is currently licensed for ocular conditions such as age-related macular degeneration and colorectal cancer. Several clinical trials have investigated the use of bevacizumab in MBC and specifically in TNBC. A number of these clinical trials have focussed on the addition of bevacizumab to currently approved chemotherapeutic regimens such as taxanes or anthracycline-based therapies with improvements in PFS and OS noted [78-82]. For example, the RAD001 clinical trial examined the use of bevacizumab in addition to epirubicin, cyclophosphamide and docetaxel and determined a significant increase in the rates of pCR among 663 patients with TNBC from 27.9% to 39.3% [83]. This response did not occur in the non-TNBC group demonstrating specificity for VEGF targeting in TNBC. In the CALGB 40603 trial, the addition of bevacizumab to a regimen consisting of paclitaxel, doxorubicin and cyclophosphamide showed an increase in pCR rates from 48% to 59% [49]. VEGF levels have also been used to predict response to VEGF-targeted therapy with high VEGF serum levels found to be predictive of good response to bevacizumab in TNBC [84].

Sunitinib is an orally available multitargeted tyrosine kinase inhibitor that inhibits VEGF as well as Platelet-Derived Growth Factor Receptor (PDGFR), c-Kit and colony-stimulating factor 1 receptor (CSF-1R) [85]. A phase II, multi-centre study of sunitinib monotherapy in MBC showed moderate activity in cancers pre-treated with anthracyclines, with a response rate of 15% in TNBC [86]. However, a follow up phase III trial has not demonstrated the use of

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sunitinib to be beneficial [87]. Two clinical trials (SOLTI-0701 and RESILIENCE) involving sorafenib, another tyrosine kinase inhibitor that inhibits VEGF signalling, have shown modest activity in HER2 negative MBC [88-90], though patients were not further stratified based on expression of ER or PR. The combination of VEGF inhibitors with bevacizumab and sorafenib has also been assessed among 18 patients (8 with TNBC) in the BRE06-109 trial [91]. This combination was deemed too toxic for further study and the trial was terminated. Results of further clinical trials will confirm whether there is a role for such agents in the treatment of MBC and TNBC.

Several investigations have revealed that the expression of VEGF in TNBC is significantly higher than in non-TNBC (54.3% *vs* 22.9%) [76,92,93]. It has also been shown that VEGFR expression is higher in metastatic breast cancer than in non-metastatic breast cancer by approximately twofold [94,95]. These findings potentially implicate VEGF involvement in the more aggressive and invasive disease progression associated with TNBC. Significant links have been established between VEGF expression and DFS/OS with high expression associated with worse outcomes [77,93]. VEGF2 has also been found to be a significant prognostic biomarker for TNBC with high expression of VEGF2 associated with decreased 5 and 10 year survival rates in a cohort of 96 TNBC patients selected from a total of 564 [96,97]. This indicates the potential for VEGF and associated receptors to be used both to inform prognosis and guide targeted therapy.

Multi-Tyrosine Kinase Inhibitors

Interest in multiple tyrosine kinase inhibitors has grown in recent times as the effort to find targeted treatments for TNBC continues. Tyrosine kinases are enzymes that are involved in the phosphorylation of various proteins, usually as part of a downstream signalling pathway. These include the Src kinases, a family of non-receptor tyrosine kinases responsible for cellular proliferation and differentiation [98]. Abnormal activity of Src kinases impacts growth, angiogenesis and migration of breast tumours [99,100]. Furthermore, Src was found to be expressed in the majority of TNBC tumours (95%) and more frequently than in non-TNBC tumours (84%) [98]. Dasatinib is a potent, orally available inhibitor of multiple tyrosine kinases such as Src, Bcr-Abl, PDGFR and c-Kit, currently approved for use in leukaemia [98,101]. A number of studies have looked at using dasatinib as monotherapy or in combination for the treatment of MBC and TNBC. Despite promising results in pre-clinical studies, dasatinib has failed to show benefit in clinical trials as a single agent in TNBC with ORR of just 4.7%, and in MBC (0% PFS at 16 weeks) [99,100]. Although single agent activity of dasatinib is limited, it appears to show potential in combination with other agents. The combination of dasatinib with cetuximab and cisplatin had a synergistic effect of growth inhibition in TNBC cell lines compared to either alone [102]. A phase I clinical trial investigated the combination of paclitaxel and dasatinib in 15 MBC cases, 6 of which were TNBC. The combination demonstrated preliminary activity, with 4 out of 13 assessable patients having a partial response and an additional 5 displaying stable disease [101]. Bosutinib, a Src/Abl tyrosine kinase inhibitor has been evaluated as a single agent in MBC in a phase II clinical trial [103]. 16-week PFS rates for these patients were 39.6% in the overall population and 25% in the TNBC subset. Despite the lower PFS rates in TNBC, the findings from this trial indicate that bosutinib showed promising antitumour activity and may warrant further investigation.

PI3K/mTOR Pathway Targeting

The PI3K/mTOR pathway is a signalling pathway responsible for cell growth, survival and cell cycle regulation [104]. Abnormal activation of this pathway has been implicated in many types of breast cancer [8] and mutations of PI3K have been found in 10-21% of TNBCs [105,106]. Lehmann BD et al. [105] found that mutations in this pathway are potential drivers of growth in the LAR subtype of TNBC, with activating mutations present in all LAR cell lines analysed. *In vitro* studies have shown that the growth of LAR-type cell lines is inhibited by dual PI3K/mTOR inhibition [8]. mTOR is an effector of this pathway and mutations are frequently found to increase its activity leading to uncontrolled cell growth [26]. Abnormal functioning of this pathway can occur by activating mutations of PI3K itself, or from mutations in negative regulators of the pathway, such as PTEN [107]. Pre-clinical studies have shown that dysregulation of the PI3K/mTOR pathway sensitises cancer cells to mTOR inhibitors [88]. Additionally, it has been found that inhibitors of PI3K may lead to DNA damage and down regulation of BRCA1/2 [107]. This disrupts the process of homologous repair and stabilises double strand breaks in DNA. This finding has led to studies of PI3K inhibitors alongside DNA damaging chemotherapy as a new approach to treating TNBC. Results of these *in vitro* studies indicate that PI3K inhibition sensitises TNBC to PARP inhibition [107] and suggests investigation in a clinical trial setting is warranted.

Everolimus and temsirolimus are orally available inhibitors of mTOR that are currently approved for the treatment of renal cancer [104]. Trials of everolimus in TNBC have been conflicting. Everolimus alongside weekly cisplatin and paclitaxel in HER2 negative MBC caused significant anti-tumour activity at a range of doses in a phase II trial of 55 patients, of which 63% were TNBC [108]. A phase II trial in 25 TNBC patients treated with everolimus and carboplatin revealed a CBR of 36%, with 1 complete response, 6 partial responses and 7 patients with stable disease [109]. Another phase II trial assessing the addition of everolimus to a regimen of paclitaxel/FEC (5-fluorouracil, epirubicin, cyclophosphamide) saw the combination therapy giving rise to higher pCR rates (25.9% *vs* 30.4%) and was well tolerated [110]. The addition of temsirolimus or everolimus to liposomal doxorubicin and bevacizumab was also beneficial, with improvements in ORR [111]. In contrast, two recent phase II trials found that the addition of everolimus to chemotherapy (paclitaxel/cisplatin, gemcitabine/cisplatin respectively) caused no increase in efficacy, but did add to toxicity [112,113]. Further clinical trials, with emphasis on the subtypes of TNBC treated, will ascertain whether this treatment approach is beneficial.

Immunotherapy

Immunotherapy is a rapidly evolving area and there is significant research involving the development of new targeted treatments and biomarkers in TNBC. The immune system plays a key role in all cancers and immunotherapy has been used successfully in a range of tumours. Evidence that the immune system plays an important role in disease progression and survival in breast cancer is abundant, given findings that infiltrates of CD8+ T cells are associated with improved outcomes in breast cancer [114], and specifically basal-like breast cancer [115]. Conversely, the presence of CD4+ T cells is linked to poor outcomes. Various TNBC sub typing studies have also identified a population characterised by high levels of immune infiltrate [7,8,17]. This suggests that an immunotherapeutic approach to treatment would be beneficial, at least for this group.

Several candidates for immunotherapy have been put forward and such agents are currently undergoing clinical and pre-clinical studies [116-118]. Studies in this area have thus far been limited to advanced disease, but as these trials progress, if efficacy is proven they have the potential to be studied in the early disease setting. One

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immunotherapeutic marker of interest is PD-L1, which upon binding to its receptor (PD-1) acts as an immune checkpoint receptor to down regulate T cell functioning [119]. PD-L1 has been found to be highly expressed in 20% of an unstratified TNBC population (N=105) and is present in higher levels than non-TNBC [120]. Pembrolizumab is a humanised monoclonal antibody that binds to PD-1, blocking its activation by its ligand PD-L1 [119]. The KEYNOTE-012 phase IIb clinical trial evaluated pembrolizumab as a single agent in patients with advanced TNBC with assessment for PD-L1 status [121]. PD-L1 status was assessed by IHC, and positivity was confirmed by stromal expression or >1% tumour expression. Of 111 TNBC patients initially assessed, 58.6% were PD-L1 positive. 32 patients were enrolled for treatment, with an ORR of 18.5% after treatment. This study led to the KEYNOTE-086 trial, which assessed pembrolizumab in pre-treated TNBC cases, regardless of PD-L1 status [122]. The ORR in this group was 5%, with the treatment regimen showing a good safety profile. The KEYNOTE trials show how stratifying patients based on the biology of their specific cancers can lead to targeted therapy that is more effective. It is likely that there is significant overlap between the immune rich TNBC subtype identified by gene expression studies, and the patients that display PD-L1 expression in the tumour tissue. Durvalumab is an IgG1 monoclonal antibody which blocks PD1/PD-L1 binding, and has been implicated in lung, bladder and other cancers [123,124]. The combination of durvalumab and the PARP inhibitor olaparib has been investigated in a range of cancers including BRCA1/2 mutant, HER2 negative breast cancers in the MEDIOLA trial [125]. Initial results show the combination of drugs is tolerable and displays preliminary efficacy in this patient group, with further study warranted [126]. There are ongoing clinical trials assessing this pathway as a target for immunotherapy in TNBC [127] and significant efforts to determine the optimal predictive biomarker for response.

Tumour vaccines have also gained interest and are being evaluated in the context of TNBC. These treatments aim to stimulate the host immune system to fight and destroy cancer cells. Tumour vaccines have the potential to be used as preventative treatment as well as therapeutically. They can contain cancer cells or antigens to evoke a host immune response. One such cancer antigen is MUC1, a cell surface based mucoprotein that is abnormally expressed or glycosylated in various cancers, including TNBC [128,129]. The combination of a MUC1 vaccine with a monoclonal antibody inhibiting cytotoxic T-lymphocyte associated protein 4 (CTLA-4) thereby acting as an immune checkpoint blocker was found to have significant *in vivo* anti-tumour activity in TNBC [130]. Another antigen of interest is NY-ESO-1, which was shown to be expressed in 16% of 168 TNBC cases in one study, with 78% of these patients showing an antibody response to the antigen [131]. This high immunogenicity makes NY-ESO-1 a promising candidate for the development of a tumour vaccine. This is a relatively novel area of research and investigations are continuing into new immunotherapeutic compounds and approaches to treat TNBC.

Immune markers also have significant prognostic value in TNBC. Key observations have shown that the presence of Tumour Invading Lymphocytes (TILs) is associated with improved survival and improved response to anthracycline based chemotherapy [128,132,133]. Additionally, as discussed previously, immune markers can be used to identify patients that will respond to various treatments, be it immunotherapy or other chemotherapies. Further clinical trials which take into account expression of immune markers such as PD-L1, may yield more significant results in stratified TNBC populations.

CDK4/6 Inhibition

Targeting of Cyclin Dependent Kinases (CDK) has recently emerged as a novel way of treating a variety of cancers; owing to their important roles in the cell cycle [134]. CDKs are enzymes that interact with cyclin subunits to phosphorylate proteins. In doing this, they can act as cell cycle regulators, ensuring progression through the cell cycle, as well as regulating processes such as transcription and apoptosis [135]. CDK4/6 interacts with cyclin D subunits to phosphorylate the Retinoblastoma protein (RB). RB is a tumour suppressor protein that negatively regulates the cell cycle. Phosphorylation of RB causes inactivation, allowing cell progression through the cell cycle. It has been shown that the loss of RB is more common in TNBC than in other breast cancer subtypes [136] and disruption of the normal function of CDK4/6 occurs in breast and other cancers [137]. The resulting unregulated cell cycle allows cells to divide uncontrollably. In this way, aberrant CDK4/6 function can drive oncogenesis and pharmacological inhibition of this has been investigated in over 20 types of cancers [137]. One of these agents, palbociclib (a highly selective CDK4/6 inhibitor) is currently approved in the treatment of ER positive breast cancer [135]. Trials of CDK4/6 inhibition in the context of TNBC have not yet reached the clinical setting but interest in this area is growing. Two recent studies have found that TNBC cell lines are sensitive to treatment with palbociclib and that this effect is synergistic when combined with PI3K inhibitors [138,139]. This combination of therapy increased cancer cell toxicity and immunogenicity. Although such studies are in their early stages, inhibition of CDK4/6 could present a novel and effective means of treating a subset of TNBC.

Conclusion

In summary, TNBC is a highly heterogeneous disease and treatment options based on a single disease result in limitations for clinical benefit and development of novel agents. There is a wide range of promising treatment approaches being investigated for TNBC. Many of these are highly efficacious when used in the correct patient populations. This review highlights both single gene and multigene signatures that must be applied to clinical practice to identify relevant treatment groups in order to allow the development of novel therapies to progress. Stratification before treatment enables a personalised medicine approach that will improve survival and management of TNBC.

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