Triple negative breast cancer: proven and promising systemic therapies

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Abstract

Triple-negative breast cancer (TNBC) is a heterogeneous disease. While simply defined by immunohistochemical parameters, TNBC actually encompasses a raft of tumour subtypes with variable prognoses and treatment sensitivities. Systemic treatment decisions for patients with TNBC are becoming increasingly complex. In many cases, decision-making remains hampered by the current lack of predictive and prognostic biomarkers, and as such, chemotherapy remains the mainstay of systemic treatment options. Sequential anthracycline and taxane regimens, delivered as either neoadjuvant or adjuvant therapy, are widely accepted as the ‘standard of care’ in early stage disease. TNBC in BRCA1 and BRCA2 mutation carriers are more likely to be sensitive to platinum-based chemotherapy and PARP inhibition. The role for these approaches is currently under investigation in large clinical trials for this population. As with certain other solid tumours, harnessing the immune system to tackle this challenging breast cancer subtype is showing some promise and the role of immunotherapy in TNBC is currently being investigated in large clinical trials. Data on safety and efficacy are eagerly awaited but will need to take into account the heterogeneous nature of this disease.

Systemic therapy options for triple-negative breast cancer (TNBC) are increasingly seen as a complex clinical conundrum. Although historical approaches have focused on chemotherapy, promising novel therapies are emerging as a result of new insights into TNBC biology and growing recognition of the heterogeneous nature of this breast cancer subtype.

Classification and clinical behaviour of TNBC

‘Triple-negative’ encompasses a diverse breast cancer subtype. TNBC is defined by immunohistochemistry as <1% immunostaining for oestrogen and progesterone receptors,1 and no HER2 protein overexpression (0 or 1+ on immunohistochemistry (IHC)) or HER2 gene amplification.2 TNBC accounts for approximately 12-17% of all breast cancers.3

When evaluated by gene expression profiling, most TNBCs exhibit a basal-like phenotype. Similarly, most (but not all) of the basal-like group are triple-negative.4,5 Six molecular subtypes of TNBC (eponymously named Lehmann subtypes) have been defined from pooled gene-expression studies: basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL) and luminal androgen receptor (LAR).5 These molecularly defined subtypes highlight the marked biological diversity within TNBC and this stratification may enable the development of targeted therapies but are not yet translatable for day-to-day management of patients with TNBC.

Although most TNBC occur in young women and are high grade, invasive ductal carcinomas with aggressive disease behaviour, TNBC can also include better prognostic subtypes of medullary, apocrine and squamous cell.6 A study published in 2006 demonstrated the significant clinical
heterogeneity in this group. The study by Haffty and colleagues found that in the absence of systemic chemotherapy after surgery, a subgroup of women with TNBC remained disease free five years following surgery. Further work is required to discover prognostic biomarkers that identify individuals with an excellent prognosis who do not require intensive adjuvant therapy as well as predictive biomarkers that help guide specific systemic therapy.

Systemic therapy options for TNBC and markers of response

Chemotherapy is currently the only recommended systemic therapy for early stage TNBC. Chemotherapy can be administered before (neoadjuvant) or after (adjuvant) surgery with no reported difference in disease free and overall survival. Neoadjuvant chemotherapy may render operable an inoperable locally advanced cancer and may allow breast conservation surgery rather than mastectomy.

The neoadjuvant approach also allows assessment of the chemo-responsiveness of the cancer in the breast and nodal tissue. A pathological complete response (pCR) can be defined as no residual invasive disease in the breast or nodal tissues. In patients with TNBC pCR correlates with favourable outcome. An important finding by Liedtke et al was that patients with TNBC have increased rates of pCR when compared to those with non-triple negative disease and pCR correlated with excellent overall survival at three years compared to those with residual disease (RD). The higher rate of pCR in TNBC likely reflects their highly proliferative nature.

More recently, Symmans et al have described the residual cancer burden (RCB) to illustrate the spectrum of residual disease. RCB can be calculated using four parameters from the post-treatment surgical specimen; the dimension of the tumour bed in the resection specimen, the proportion containing invasive carcinoma, the number of axillary nodes containing metastatic carcinoma and the largest metastasis in an axillary node. The parameters of the RCB index were found to be individually associated with significantly higher risk of distant relapse in a cohort of 241 women (and validated in a further 141) who had neoadjuvant anthracycline and taxane chemotherapy.

There is currently no clearly preferred regimen of chemotherapy for patients with TNBC compared with non-TNBC. Evidence to date is largely derived from retrospective, sub-group analyses with relatively small patient numbers and suboptimal power to enable definitive treatment recommendations. Most large adjuvant chemotherapy studies were undertaken prior to our current understanding of biological subtypes and the results therefore derived from biologically heterogeneous breast cancer populations. Given the aggressive nature of the TNBC phenotype as a whole, the current recommendations for TNBC are polychemotherapy with sequential anthracycline (such as doxorubicin or epirubicin) and taxane (paclitaxel or docetaxel) in various well-described regimens.

Platinum-based systemic therapy

The role of DNA-damaging platinums (such as carboplatin and cisplatin) in treatment of early TNBC is still undefined. There are pre-clinical and clinical reports of exquisite platinum sensitivity in tumours with defective double strand DNA repair, such as that mediated by BRCA1 or BRCA2 mutations. A hallmark feature of BRCA1 and BRCA2-associated tumours is defective homologous recombination DNA repair and over 75% of invasive breast cancers arising in BRCA1 mutation carriers are TNBC. The overlap between BRCA1-associated cancers and TNBC has created much interest in whether platinums may also improve outcomes in non-BRCA mutated sporadic TNBC.

In a single arm, phase II trial of 28 women with TNBC, Silver et al reported that single agent neoadjuvant cisplatin (75 mg/m2 q21 x four cycles) resulted in pCR in 6 (21%) women. The two BRCA1 mutation carriers enrolled on trial achieved pCR and lower BRCA1 mRNA expression was significantly associated with a larger percentage of patients achieving a good response.

In the randomised open-label, phase II neoadjuvant trial, GEICAM 2006-03 in basal-like TNBC (defined by the presence of CK5/6- or EGFR-positive cells by immunochemistry), Alba et al reported on neoadjuvant epirubicin and cyclophosphamide, followed by docetaxel with or without carboplatin (AUC6 q21). Both treatment arms (94 patients) had a pCR rate of 30%. Carboplatin was associated with more anaemia and thrombocytopenia. Unfortunately the statistical design did not allow...
comparison between the arms and response was not stratified in terms of BRCA1/BRCA2 mutation carrier status or tumour ‘BRCA-like’ features.

In the randomised phase II trial, GeparSixto, patients received weekly pegylated anthracycline, taxane and bevacizumab. Within the TNBC group, patients (n=315) were further randomly assigned to receive weekly carboplatin (AUC 2, dropped to AUC 1.5 after interim safety analysis) or placebo. The addition of carboplatin led to a statistically significant higher pCR of 53% versus 37% in the placebo arm. Treatment discontinuation was high in both arms (48% in the carboplatin arm and 39% in the placebo arm), largely due to therapy-related toxicities. This improvement in pCR correlated with improved disease free survival. However a criticism of this study is that the platinum was added to non-standard chemotherapy; omission of an alkylating agent (cyclophosphamide) in the control arm raises the question of whether the platinum improved outcomes only because the alkylating agent was absent.

The phase II open label 2x2 factorial design CALGB 40603 trial did assess the addition of carboplatin to a standard neoadjuvant backbone of sequential anthracycline and taxane chemotherapy. Patients were randomised to receive weekly paclitaxel followed by dose-dense doxorubicin and cyclophosphamide versus the addition of carboplatin (AUC6 q21 concurrent with paclitaxel) and/or bevacizumab. Patients in the carboplatin-containing arms experienced a statistically significantly higher pCR compared to the non-carboplatin-containing arms (54% versus 41%, p=0.003) but this improvement in pCR did not correlate with improved long-term outcome. In the absence of improved long-term outcome, the addition of carboplatin is not yet supported as a standard of care.

In advanced TNBC, the TNT study was designed to test the hypothesis that impaired DNA repair mechanisms confer greater sensitivity to platinum agents than to taxanes. This randomised, phase III trial compared single agent carboplatin (AUC 6) versus doctaxel (100 mg/m²) every 21 days for six-eight cycles (or until progression) in patients with recurrent locally advanced TNBC, metastatic breast cancer or known BRCA1 and BRCA2 mutation carriers (with any hormone- and HER2-receptor status). The study found no evidence for benefit with carboplatin over docetaxel in unselected populations of patients with advanced TNBC. However, patients with germline BRCA1 and BRCA2 mutation had improved disease-free survival with carboplatin.

The findings in the TNT study appear consistent with those of Silver et al and are both indicative of the need to prospectively identify patients with tumours that harbour DNA repair defects to select them for appropriate therapy. Up to 25% of sporadic breast cancer may show a ‘BRCA-ness’ phenotype, through epigenetic inactivation of BRCA1 (through hyper-methylation) and FANCF (via methylation) and BRCA2 inactivation via EMSY amplification. There are considerable efforts underway to identify mechanisms and biomarkers for sporadic tumours that exhibit BRCA-ness and to utilise this vulnerability to target therapy.

The management of residual disease

A challenging clinical scenario is a TNBC patient with residual disease following neoadjuvant chemotherapy. It is known that non-pCR is associated with poor outcome with high chance of relapse and death within three years. It is not currently known how to improve outcomes. This scenario will become more prevalent as more patients receive neoadjuvant chemotherapy.

A trial specifically examining adjuvant chemotherapy in HER2 negative breast cancer patients with residual disease post neoadjuvant chemotherapy is the collaborative Japanese and Korean breast cancer trials group trial, CREATE-X. This phase III, double-blind, randomised trial compared capecitabine (2,500 mg/m²/d for 14 days, q21 for eight cycles) versus placebo. Approximately one third of patients in the study had TNBC. Patients with hormone positive breast cancer also received adjuvant endocrine therapy. Capecitabine improved disease-free survival (74.1% vs 67.7% HR 0.70) and overall survival (94% vs 89.2% HR 0.60). This benefit from capecitabine is in contrast to other studies that have shown no benefit from the addition of capecitabine to neo or adjuvant chemotherapy, however this study is unique in design as it is assessing a sub-selected population of patients with residual disease following standard therapy.

Promising data have also emerged from the International Breast Cancer Study Group (IBCSG) Trial 22-00, which compared low-dose oral cyclophosphamide (50 mg/d continuously) and oral
methotrexate (2.5 mg/d day 1, 2 every week) for one year as maintenance adjuvant therapy versus no treatment in hormone-receptor negative breast cancer. This treatment commenced after surgery and standard adjuvant chemotherapy. The trial found that the subgroup of women with node positive TNBC had the greatest benefit (albeit not statistically significant) in terms of five-year disease-free survival, with 71.9% in the treatment group versus 64.2% in the control. This trial was not in patients with residual disease after neoadjuvant chemotherapy but it did identify a promising metronomic combination that warrants further investigation in high-risk patients.

While both the CREATE-X and IBCSG 22-00 trial hold promise, the inclusion of adjuvant therapy in patients with residual disease following neoadjuvant therapy as a standard of care requires further follow up and publication of mature data from these trials.

**PARP inhibition**

An intriguing clinical target in TNBC is the enzyme, poly adenosine diphosphate ribose polymerase, (PARP). The role of PARP inhibitors is currently being evaluated by a number of rigorous, well-designed clinical trials.

Cells with compromised DNA damage repair are vulnerable. As previously described, *BRCA1* and *BRCA2* deficient cells have impaired homologous recombination. Exposure of these deficient cells to a PARP inhibitor can result in catastrophic mutations and cell death. This is an example of synthetic lethality, when mutation (or inhibition) of two (or more) repair pathways provokes cell death.

A phase I trial established that the PARP inhibitor, olaparib, was well tolerated, and had anti-tumour efficacy in *BRCA1* and *BRCA2* mutation carriers. *BRCA1/2* mutation carriers with advanced, recurrent breast cancer were treated with olaparib. Of the patients with TNBC, response rates were 25% and 54% in lower and higher dosing cohorts respectively. The study provided positive proof-of-concept that olaparib has clinically relevant activity in BRCA-associated TNBC.

The SOLACE phase I trial is currently underway to determine the maximum tolerated dose of olaparib in combination with low dose cyclophosphamide in advanced *BRCA*-associated breast cancer and TNBC (ACTRN12613000924752). This is a study conducted by the Australia New Zealand Breast Cancer Trials Group (ANZBCTG) and is due to report soon.

Olympia (NCT02032823), is a randomised, double blind, placebo-controlled phase III study evaluating adjuvant olaparib in *BRCA1/2* mutation carriers who have completed neoadjuvant chemotherapy, but did not achieve a pCR or had high-risk disease and have completed adjuvant therapy. Olaparib (300 mg BD) versus placebo is administered for 12 months. The primary outcome is invasive disease-free survival and recruitment is ongoing, including in Australia via the Australia New Zealand Breast Cancer Trials Group.

Another PARP inhibitor, veliparib, has also been shown to have activity in *BRCA1/2* mutation carriers with metastatic breast cancer when combined with temozolamide. BROCADE3, a phase III randomised, placebo-controlled trial of carboplatin and paclitaxel with or without veliparib in metastatic HER2 negative or locally advanced unresectable *BRCA*-associated breast cancer is currently recruiting patients. The trial is designed to determine clinical benefit in terms of progression-free survival and will provide important insights into treatment of *BRCA*-associated breast cancers.

The roles of carboplatin and PARP inhibition in addition to standard chemotherapy are currently being studied in the neoadjuvant BRIGHTNESS trial (NCT02032277). This three-arm, randomised, placebo-controlled, double blind phase III study is evaluating pCR following neoadjuvant paclitaxel +/- carboplatin +/- PARP inhibitor veliparib followed by doxorubicin and cyclophosphamide. Patients are stratified by *BRCA1/2* status. The results of BRIGHTNESS are eagerly awaited. BRIGHTNESS follows on from I-SPY 2, which showed promise when carboplatin and PARP inhibition were added to standard chemotherapy.
TNBC and the immunotherapy age

Harnessing the immune system for the treatment of TNBC, like other solid-organ malignancies, is compelling. In node positive TNBC increased lymphocyte infiltration of the tumour and adjacent stroma are significantly associated with a good prognosis, regardless of chemotherapy type. In addition, tumour-infiltrating lymphocytes can predict improved pCR.

Tumours can utilise the PD-1/PD-L1 pathway to avoid immune surveillance and promote neoplastic growth. Keynote 012 was a single arm trial of anti PD1 (pembrolizumab) in heavily pre-treated TNBC. Overall response rate was 18.5% and toxicities were generally mild. The Lehmann IM subtype of TNBC contains gene sets rich in immune signaling pathways and this subtype may represent a responding cohort. Ongoing trials are evaluating the role of immunotherapy as a single agent and in combination with chemotherapy in TNBC.

Conclusion

We are in an exciting era where insights into the biology and heterogeneity of TNBC are providing new biomarkers and therapeutic targets that are likely to be increasingly exploited to treat this clinically challenging subtype of breast cancer. It is becoming increasingly clear that determining the BRCA1/2 mutation status of patients could inform their clinical management. Current studies will elucidate the role of platinum, PARP inhibitors and immunotherapy.

References


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