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Towards new therapies for triple negative breast cancer (TNBC)

As gene sequencing and other technologies start to reveal the diverse nature of TNBC, new subtype-specific therapies can emerge

Most women presenting with breast cancer have hormone driven cancers and endocrine treatments form the cornerstone of their care. About 20 per cent of patients have HER2-positive breast cancers and over the last decade anti-HER2 therapies have changed the natural history of this cancer type beyond all expectations. The remaining women have breast cancers that are not driven by oestrogen or HER2 and these cancers are referred to as triple negative breast cancer (TNBC). Triple negative breast cancer is characterised immunohistochemically by its lack of expression of oestrogen receptor, progesterone receptor and HER2. It is associated with a younger age at diagnosis; African-American ethnicity; and germline mutations in BRCA 1.

The lack of a target for treatment and the inherently aggressive clinical behaviour of these cancers explains the relative poorer clinical outcome compared to the other breast cancer types. Chemotherapy remains the primary established treatment option for TNBC in the early and advanced settings. The risk of relapse after treatment of early stage TNBC peaks in the first three years after diagnosis and this is followed by a sharp decline in risk. This type of breast cancer has a tendency to relapse in viscera, ie, lung, liver, and brain, with bone metastases being less common.

Triple negative breast cancer describes a clinically and molecularly heterogeneous group of cancers. Widespread use of "omic" technologies (genomics, transcriptomics, proteomics, etc) has identified distinct subgroups within TNBC distinguishable by their clinical behaviour, responses to standard chemotherapy drugs and the presence of potential targets for treatment. Lehmann *et al* using gene expression profiling identified six subtypes of TNBC: two basal-like related (basal-like 1 [BL1] and 2 [BL2], two mesenchymal-related (mesenchymal [M] and mesenchymal stem-like [MSL]), one immunomodulatory group (IM) and one luminal androgen receptor (LAR) group.

The basal-like term was given because tumour cells express genes characteristic of normal basal/myoepithelial cells such as cytokeratin 5 and 17 and EGFR. However, even basal-like breast cancer is a heterogenous group. Most basal-like breast cancers are triple negative and not all TNBC is basal-like.

The luminal androgen receptor (LAR) group although immunohistochemically is triple negative, histologically and genetically it is similar to hormone receptor-positive breast cancer. It is also characterised by the expression of androgen receptor (AR). The immunomodulatory subgroup is characterised by a strong immune and inflammatory signature. Mesenchymal and mesenchymal-like groups share similar features with metaplastic breast cancer.

The response rates to preoperative chemotherapy depends on the TNBC subtype. While overall for TNBC the pathological complete response rate (pCR), ie, the absence of invasive breast cancer in the breast or axillary lymph nodes after preoperative chemotherapy is 28 per cent when examined by subtype the highest pCR rate is seen in BL2 breast cancer at 52 per cent with rates of 0 per cent, 10 per cent and 23 per cent for BL2, LAR and MSL respectively. Gene signatures to classify TNBC into these subtypes are not in routine clinical use yet but would obviously have a valuable role in predicting which TNBC is most likely or unlikely to respond to neoadjuvant therapy.

BRCA mutation and BRCAness

BRCA1 and BRCA 2 are tumour suppressor genes that encode for proteins essential for cell division, DNA error control, DNA repair and apoptosis. BRCA 1 and BRCA 2 are required for repair of DNA double strand breaks by homologous recombination. Tumours arising in individuals with a BRCA1 germline mutation are very similar molecularly to basal-like sporadic tumours, ie, high grade, ER/PR negative, and HER2-negative. Individuals with sporadic basal-like cancers often have ineffective BRCA gene function as a result of promoter methylation, gene deletion or somatic mutations in BRCA 1/2. Both sporadic and BRCA 1 mutation-associated basal-like TNBC are sensitive to DNA damaging agents which can be exploited therapeutically.

The triple negative paradox

Despite the lack of a therapeutic target and the overall worse prognosis, patients with TNBC have higher response rates to chemotherapy and this is referred to as the triple negative paradox. Anthracycline and taxane-based chemotherapy regimens remain the most important chemotherapeutic agents in the adjuvant and neoadjuvant settings. In the metastatic setting despite optimal chemotherapy, fewer than 30 per cent of women with metastatic TNBC survive five years and virtually all die of their disease.

Combinations of chemotherapeutics may offer higher response rates but this comes with increased toxicity and no proven improvement in survival. International guidelines recommend single agents except in the setting of rapidly progressing disease or a visceral crisis. The role of platinum-based chemotherapy has been studied in TNBC due to the intrinsic genomic instability of a subset of TNBC due to deficient DNA repair. The

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TNT trial randomised 376 patients with metastatic TNBC to carboplatin versus docetaxel. The overall response rates were similar between the two agents, however, in patients with a BRCA 1/2 there was a doubling of overall response rates for platinum (68 per cent) compared to docetaxel (33 per cent).

In the neoadjuvant setting there are data from randomised trials indicating an improvement in pCR with the addition of a platinum to standard anthracycline taxane regimes, however, whether this will translate into a long-term improvement in disease-free and overall survival is unknown and these studies unfortunately are not powered for these endpoints. Cancer Trials Ireland will begin to participate in an international clinical trial in the coming months that will examine the addition of carboplatin to standard adjuvant chemotherapy in women with TNBC.

PARP inhibitors and Synthetic Lethality

Poly-ADP-ribose polymerase (PARP) is an abundant constitutively-expressed nuclear enzyme involved in DNA repair. At sites of DNA damage PARP activates intracellular pathways that modulate DNA repair. BRCA 1/2 deficient cells are extremely sensitive to PARP inhibition, which results in DNA double strand breaks in replicative cells. In BRCA-deficient cells homologous recombination is impaired, thus, these cells rely on PARP functionality for repair. Inhibition of PARP by PARP inhibitors leads to severe highly selective toxicity in BRCA 1 and BRCA 2 defective cells and this is referred to as synthetic lethality. There are several clinical trials investigating the PARP inhibitor olaparib in the metastatic and neoadjuvant settings. Cancer Trials Ireland is currently participating in a clinical trial where patients with metastatic breast cancer who carry a mutation in BRCA 1 or 2 are randomised to standard chemotherapy versus the PARP-inhibitor talazoparib.

Anti-Androgen Blockade

The luminal androgen receptor (LAR) subtype of TNBC has shown sensitivity to AR antagonism in vivo and in vitro. Cancer Trials Ireland recently enrolled patients on a Phase II study with enzalutamide a potent AR antagonist in women with metastatic AR positive TNBC. In the 75 patients evaluable there were two complete responses and five partial responses.

An androgen receptor gene signature has been developed to predict patients with a higher likelihood of response, but further validation of the signature is required.

The immune system and TNBC

The higher mutational burden and genomic instability of TNBC results in a propensity to generate neo-antigens which can be recognised as non-self by the adaptive immune system. Compared to other breast cancer subtypes TNBCs have higher tumour infiltrating lymphocytes (TILs). Higher TILs have been associated with lower risk of relapse in breast cancer. High levels of expression of immune markers have also been associated with chemotherapy benefit in TNBC. There are very consistent data showing a strong association between high TILs and lower risk of relapse in chemotherapy-treated patients. Prospective trials will determine if patients with TNBC could potentially be stratified into those with TNBC with a 'hot' immune environment and associated with a better prognosis and higher likelihood of chemotherapy benefit compared to those with a 'cold' immune environment, a worse prognosis and lower likelihood of response to standard chemotherapy.

The findings that some TNBC is immunogenic has provided the rationale to study immunotherapies. Two Phase I trials have reported using checkpoint inhibitors in advanced TNBC. In PDL1-positive TNBC the anti-PD1 antibody pembrolizumab had a response rate of 18.5 per cent. Further international randomised studies include a trial of pembrolizumab versus standard chemotherapy in metastatic unselected TNBC being run through Cancer Trials Ireland. A neoadjuvant study is about to begin in cancer centres across Ireland that will randomise patients with early TNBC to preoperative carboplatin and nab-paclitaxel carboplatin +/- atezolizumab. Early data using this combination in the metastatic setting has shown very high response rates.

Conclusion

Gene sequencing technologies have begun the painstaking process of unravelling the complex molecular landscape of triple negative breast cancer. It is very clear that TNBC is comprised of many disease entities. Unfortunately, the current immunohistochemical definition of TNBC used in the clinic today is inadequate and does not capture the molecular or clinical complexity and diversity of this elusive disease.

As this field of research progresses, better classifications should lead to TNBC subtype-specific therapy. Tumours with BRCA 1/2 aberrations or defects in homologous recombination (BRCAness) should be considered for PARP-inhibitor therapy trials and also might benefit from a platinum agent. Actionable mutations are rare in TNBC, nevertheless adaptive clinical trials are in progress to evaluate agents targeting PI3K/mTOR, RAS/RAF/MEK pathways. Immune checkpoint inhibitors are now a standard of care for many cancer types with incredible results. It is very likely that they will play a pivotal role in the treatment of this difficult group of breast cancers in the near future.

For further information about clinical trials in TNBC or other breast cancer types please visit www.cancertrials.ie.

References on request

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