

Leading Article

Triple-negative breast cancers – update in classification and biomarker profile

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Introduction

Invasive breast carcinoma (IBC) is a heterogeneous disease, with more than 20 distinct histologic types recognized by the World Health Organization (WHO) classification (1). In addition to immunohistochemical (IHC) methods, molecular techniques have yielded information on the genetic characteristics of IBC by gene expression profiling (GEP), adding another perspective onto IBC classification. Five intrinsic subtypes of IBC: luminal A, luminal B, normal breast-like, HER2-enriched, and basal-like have been identified, with demonstrable

correlation with patient demographics, disease biologic behaviour and response to treatment (2, 3, 4).

In routine clinical practice, molecular classification by GEP is frequently replaced by IHC surrogate. Despite less than perfect concordance (5), IHC classification is now a common accompaniment to morphologic assessment. The 2013 St. Gallen consensus guideline elaborates molecular classification based on IHC markers, namely oestrogen receptor (ER), progesterone receptor (PR), HER2 and Ki67, and classified as: luminal A-like (ER+, PR \geq 20%, HER2-, Ki67 <20 %), luminal B-like (ER+, PR<20% and/or HER2+ and/or Ki67 \geq 20 %), HER2 over-expressed (ER-, PR-, HER2+) and basal-like(ER-, PR-, HER2-) [6]. IHC typing subsequently guides hormonal and HER2 targeted adjuvant therapies (7, 8, 9).

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Triple negative breast cancer (TNBC)

TNBC is characterized by the lack of ER, PR and HER2 expression by IHC analysis (10), constitutes 10%-20% of all breast cancers (11), occurs more frequently in younger patients (11,12,13), is associated with a higher tumour grade and a higher risk of distant recurrence and disease-related mortality within the first 3-5 years after diagnosis (14,15). TNBC, similar to the basal-like breast carcinoma (BLBC) in the GEP molecular classification, shows a significantly shorter survival following the first metastatic event when compared with those with non-basal-like/non-triple-negative controls (16, 17). Histologically, TNBC is heterogeneous and encompasses many different histologic subtypes in the current WHO classification. TNBCs may appear as infiltrating duct carcinoma no special subtype, carcinoma associated with BRCA-1 mutations, carcinoma with medullary features, pleomorphic lobular carcinoma and apocrine carcinoma. In addition TNBC can also be low grade and associated with good prognosis, and includes rare tumours like adenoid cystic carcinoma and secretory carcinoma. In addition, it has been shown that there is significant intratumoral heterogeneity in TNBC (18). These evidence indicated that TNBC should not be treated as a single disease, but a group of diseases with different biologic behavior. Further sub-classification and evaluation of novel markers may be useful in better defining TNBC and for their accurate prognostication, and potential treatment strategies.

Molecular classification of TNBC

Further molecular stratification of TNBC by mRNA profiling and DNA and mRNA profiling have yielded similar subtyping results with subtypes showing unique biological and clinical behavior (19, 20). Indeed there is significant overlap between mRNA and DNA profiling stratification, and currently, four major TNBC subtypes have been identified, namely luminal androgen receptor (LAR), mesenchymal (MES), basal-like immunosuppressed (BLIS), and basal-like immune activated (BLIA) (20).

LAR subtype exhibits activation of pathway pertaining to androgen receptor (AR), ER, prolactin and ErbB4 signaling, and GEP demonstrates upregulation of ESR1 and other oestrogen-regulated genes (PGR, FOXA, XBP1, GATA3). LAR subtype also exhibits broad and focal copy number changes with amplification of CCND1 and FGFR2 genes. For the MES subtype, there is upregulation of genes related to cell cycle, mismatch repair and DNA damage networks, as well as hereditary breast cancer signaling pathways. MES subtype also highly expresses osteocyte (OGN) and adipocyte (ADIPOG, PLIN1) exclusive genes and insulin growth factors (IGF1). The BLIS subtype exhibits down-regulation of immune-regulating pathways and cytokine pathways, with low expression of molecules controlling antigen presentation, immune cell differentiation and innate and adaptive immune cell communications. Of note, BLIS subtype uniquely expresses SOX family transcription factors

compared to other TNBC subtypes. Contrary to the BLIS subtype, BLIA subtype exhibits up-regulated immune-regulating pathways and basal like cluster genes, with STAT transcription factor mediated pathways and high expression of STAT genes (20).

Comparing with PAM50 molecular classification, LAR subtype contains luminal A, luminal B and HER2 over-expressed IBCs, MES contains BLBCs and normal-like IBCs, whereas BLIS and BLIA are entirely BLBCs (20). These TNBC subtypes differ in prognosis and response to treatment (19), with BLIS showing the worst disease-free survival (DFS) and disease-specific survival (DSS) (20).

Additional markers relevant to TNBC classification and prognostication

Ki67

Ki67 is a nuclear antigen which is expressed in the cell cycle except the G₀ phase. Ki67 IHC staining has been used for measuring and monitoring tumor proliferation in standard pathology specimens (21). However, Ki67 IHC staining suffers from poor agreement on its precise clinical uses, heterogeneity and variable level of validity in methods of assessment and unreliable specific cutoffs often requiring validation with results from local practice (22). The current application of Ki67 IHC on IBC is mostly on segregation of luminal A and luminal B subtypes along with a panel of IHC (22). Within TNBC cases, high Ki67 expression is associated with a shorter relapse-free survival

and overall survival, but a higher response rate to neoadjuvant chemotherapy (23).

p53

The tumor suppressor p53 protein is rapidly degraded and has a very short half-life in a normal cell. Abnormal p53 accumulation is usually due to a missense mutation resulting in protein stabilization and resistance to degradation, which is then detectable by IHC methods. IHC expression of p53 has been proposed by some authors to classify TNBC into two biologically distinct subgroups – a p53-negative normal-like subgroup, and a p53-positive basal-like subgroup with worse overall, event-free survival (24) and poor response to adjuvant chemotherapy (25).

Androgen Receptor (AR)

AR is a member of the steroid hormone receptor family. Expression of AR is found in metaplastic apocrine cells of normal breast tissue and generally AR is highly expressed in all IBCs, ranging from 91% in luminal A to 59% in HER-2 over-expressed IBC (26). AR expression appears to play different prognostic roles in subsets of IBCs stratified by ER status. In ER-positive IBCs, AR expression was associated with favourable clinicopathologic features and longer DFS, whereas in ER-negative IBCs, AR expression was associated with lower survival rates (27). Among all molecular subtypes, TNBC showed the lowest (21.2%) AR expression compared to other IHC surrogate subtypes (28), but those AR expressing TNBC had better DFS (28). AR expression in TNBC also has therapeutic

implications. Bicalutamide, an anti-androgen, was found to have a clinical benefit rate of 19% in AR-, ER-/PR- metastatic BC (29).

Tumour-infiltrating lymphocytes (TIL)

It is increasingly recognized that cancers are not merely autonomous masses of mutant cells, rather it is a disease encompassing multiple components of tumor cells and host stromal cells (30). Ample evidence demonstrated that stromal cells in the tumour microenvironment are needed for the optimal tumour cell growth (30). Among them, notably, the immune inflammatory cells represent a significant component of the tumor microenvironment (30). The role of immune system in tumor progression was traditionally believed to be a counter force to tumor progression by destroying neoplastic cells. Transformed cells initiate inflammatory signals leading to recruitment of immune cells. Activation of innate immunity readies adaptive immunity. Subsequent activation of adaptive immunity elicits anti-tumor responses through T-cell-mediated toxicity in addition to antibody-dependent cell-mediated cytotoxicity and antibody-induced complement-mediated lysis (31). When normal cells transform into cancer cells, the novel tumor specific/associated antigens produced would elicit immune response. Patrolling immune cells continuously provide body wide surveillance, targeting and eliminating cells that undergo malignant transformation. Tumors develop when this immune surveillance breaks down or is overwhelmed (31). Nonetheless, recruitment of

immune cells could be a double-edged sword, as very often pro-tumor soluble molecules are often released resulting in increased risk of cancer development. These soluble molecules may provide a survival advantage to evolving cancer cells by maintaining proliferative signaling, blunting cell death in response to matrix detachment, activation and maintenance of angiogenesis (31).

A meta-analysis on the prognostic value of TIL in TNBC involving eight eligible studies with 2987 patients (32) demonstrated progressive reduction in the risk of recurrence, distant recurrence and death in proportion to increments in TIL enrichment. An association of longer survival with high TIL was reproduced regardless of location and phenotype of the TNBC, and both haematoxylin and eosin (H&E) and IHC methods of TIL interpretation demonstrated prognostic value (32). Furthermore, high TIL was associated with better response to neoadjuvant chemotherapy (33).

Programmed death 1 receptor (PD-1) and programmed cell death 1 ligand (PD-L1)

PD-L1 is constitutively expressed on all haematopoietic cells and most non-haematopoietic cells, whereas PD-1 is expressed on activated T cells, B cells, natural killer (NK) cells and myeloid cells. PD-1/PD-L1 interaction is an immune check point contributing to the maintenance of tolerance. PD-L1 expression was found in 58.6% of TNBCs and was proposed to be an immunotherapeutic

target for TNBC (34). An early trial on 27 patients with advanced TNBC has shown an overall response of 18.5% to Pembrolizumab, an anti-PD-1 agent (34). In addition, expression of PD-L1 appears to stratify BLBCs into different biologic subgroups (35), with PD-L1 high BLBC showing better metastasis-free survival (36).

Relationship with basal-like breast cancer (BLBC)

Most TNBC display a basal-like transcriptome, and most BLBC exhibit a triple negative phenotype. Thus triple negativity is commonly used as surrogate definition for BLBC (6, 10, 37) despite a less than perfect concordance. An interesting study demonstrated only partial overlap between PAM50 defined BLBC, IHC defined BLBC and morphologically defined BLBC, with an overall concordance of all differently defined BLBC at only 11%. Of note, only 59% of IHC defined BLBCs were also defined as BLBC by PAM50 (38). To produce better approximation of IHC basal (in addition to triple negativity) many additional 'basal' markers have been proposed. Among these basal cytokeratin (CK) 5/6+ and/or epidermal growth factor receptor (EGFR+) were most widely accepted and using a five-marker-based IHC surrogate of BLBC (ER-, PR-, HER2-, CK5/6+ and EGFR+) was better able to define BLBC than triple negativity alone (37, 39), achieving a 76%-79% sensitivity and 72%-100% specificity against GEP defined BLBC (37, 40). It is thus apparent that the IHC surrogate definition of TNBC can be further improved, and

this has indeed generated intense research interest. Many other IHC surrogate definitions have proposed subsequently, with varying degrees of accuracy.

Alpha B-crystallin

Alpha B-crystallin functions as a member of the conserved small heat shock protein which confers protection against a broad range of apoptotic stimuli (41). Alpha B-crystallin expression is restricted to myoepithelial cells in normal breast tissue, proliferative lesions and in situ IBCs (42). Cytoplasmic expression of α B-crystallin is demonstrated on most basal-like and metaplastic cancers (42, 43), in addition to other epithelial tumors (44). Consistent α B-crystallin gene expression is also detected in BLBC cluster from microarray studies (45). In IBCs, expression of α B-crystallin is associated also with lymph node involvement (39), shorter disease specific survival (45), and poorer overall response rates to neo-adjuvant chemotherapy (46).

FOX C-1

FOX C-1, a member of forkhead transcriptional factor, is crucial for normal development of multiple organs (47). It is expressed in normal mammary luminal progenitor population and basal/myoepithelial cells of normal terminal ductal lobular units (TDLU) [48]. Over-expression of FOX C-1 is found in various human carcinomas including IBC (49), and is associated with increased epithelial-mesenchymal transition, cell proliferation and migration (49) and poor

disease outcome (50). FOXC-1 over-expression is a consistent feature of BLBC compared with other molecular subtypes of breast cancer (51) and a two-tier IHC/quantitative real-time polymerase chain reaction (qRT-PCR) assay has been suggested as a simple and accurate single diagnostic marker of BLBC (50).

Conclusion

TNBC is a heterogeneous group of disease, consisting mostly of high grade IBCs. Effective oncologic treatment is hampered by their lack of response to hormonal therapy or agents targeted at HER2. Progression is being made in the further understanding the tumor biology, identifying potential markers of treatment relevance and prognostic stratification.

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