

Morphologic and molecular characterization of triple negative breast carcinoma for identification of clinically relevant subtypes

Introduction: Breast carcinoma is the most common malignancy in women worldwide, and the number one cause of cancer death in women. Despite the recent advances in breast cancer diagnosis and treatment, a problem is still posed by the so called 'triple negative breast carcinomas' (TNBCs). These tumours are associated with poor prognosis and are unlikely to respond to hormonal or anti-HER2 therapy. TNBCs are grouped together despite the clear heterogeneity within the subtype; there is no widely accepted evidence-based and clinically relevant way to sub-classify them. Neither is there any standard form of targeted therapy for the disease. Epidermal growth factor receptor (EGFR) is being investigated as a potential target for treatment of TNBC. The purpose of this study was to try to identify clinically significant morphologic and/or immunophenotypic subtypes within the triple negative group of breast carcinomas. We also aimed to study the associations between EGFR changes and TNBC phenotype and clinical behaviour.

Materials and methods: We performed an immunohistochemical (IHC), in situ hybridization and histomorphological study on a set of 52 archive cases of pre-treatment TNBC. Immunohistochemical expression of the following 'basal' markers was assessed: p-cadherin, p63, CD10, CK5/6, HMW and EGFR; we also assessed immunohistochemical expression of luminal marker CK18. Dual in situ hybridization was performed to detect EGFR gene copy number changes. Clinical data obtained from patients' clinical charts were compared with morphology and molecular marker status for determining possible links between tumour phenotype and clinical behaviour.

Results and Discussion: We observed a wide variation in the clinical behaviour and outcome of different cases of TNBC showing that assigning a blanket 'poor' prognosis in all cases is misleading and could result in overtreatment of patients that may not need aggressive adjuvant therapy.

All of our TNBCs expressed at least one basal marker. Only two tumours did not express CK18. EGFR protein expression was observed in 88.5% of cases. While 8 (15.4%) tumours had ≥ 4 EGFR gene copies per cell, EGFR gene amplification was seen in only 1 case.

The molecular markers and morphological characteristics we investigated were not useful in providing a basis for clinically relevant classification of TNBC. Identification of the basal-like phenotype, using varied IHC definitions, had no clinical impact. Based on our findings, we recommend a combinatorial approach to prognostication in TNBC using simple tools such as the Nottingham Prognostic Index, as this showed a statistically significant association with outcome ($p=0.036$).

We were not able to demonstrate that EGFR changes are associated with poor outcome, making us question the suitability of EGFR as a therapeutic target for TNBC. The observation of a statistically significant link between high EGFR gene copy number (≥ 4 copies per cell) and good outcome ($p=0.036$) makes us further doubt that blocking the action of EGFR in TNBCs will produce favourable results. Instead, we propose that high EGFR copy number should be further investigated as a potential marker of good outcome in TNBC.