RESEARCH ARTICLE

Prognostic markers in quadruple negative breast cancer

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ABSTRACT
Quadruple-negative breast cancer (QNBC) presents with negative expression of estrogen, progesterone, and androgen receptors and of human epidermal growth factor receptor 2. This BC subtype has the worst prognosis. In QNBC, there is a greater paucity of prognostic biomarkers than in androgen receptors-positive triple negative BC (TNBC). Absent androgen receptor expression confers a more aggressive QNBC course and correlates with the expression of cancer stem cell phenotype, COX-2, and basal markers such as CK5 and nestin. Basal-like phenotype is significantly associated with adverse prognostic markers including high KI-67, COX-2 expression, and cancer stem cell phenotype. Engrailed-1 expression is associated with unfavorable overall survival in QNBC patients. Non-coding ribonucleic acids play a significant role in BC tumourigenesis by virtue of their oncogenic and tumour-suppressive properties. The identification of QNBC-specific circulating microribonucleic acids may improve tumour detection and prognosis. There is an obvious necessity to intensify the problem-oriented interdisciplinary research on the hot topic of prognostic biomarkers of QNBC.

Key words: quadruple negative breast cancer, triple negative breast cancer, androgen receptor expression, biomarkers, prognosis

Introduction

Breast cancer (BC) is one of the leading causes of cancer-related deaths worldwide (Paul & Banerjee, 2022). Triple-negative BC (TNBC) is the most malignant and lethal subtype of this socially significant neoplasm and accounts for 10-20% of all breast cancer deaths.

Nowadays quadruple negative BC (QNBC), lacking the expression of estrogen, progesterone, human epidermal growth factor receptor-2, and androgen receptors, is considered a clinically relevant BC subtype with the worst prognosis (Huang et al., 2020).

In a review paper, QNBC is identified against androgen receptor-positive TNBC (Christenson et al., 2018). The difficulties in monitoring the androgen receptor protein concentrations, the new methods for determining the androgen receptor status as well as the role of the androgen receptors in the regulation of the immune system are comprehensively discussed.

Increasing evidence supports the essential role of the androgen receptor, a nuclear hormone receptor, in BC and at present, this receptor is considered a useful prognostic biomarker depending on the context of BC subtypes (You et al., 2022). The concept that the androgen receptor modulates BC growth and progression is currently undeniable (Di Leone et al., 2021). This receptor may act alone or in combination with other effectors participating in intracellular signaling pathways.

The purpose of this concise review is to summarize the recent literature available devoted to some essential peculiarities, biomarkers, and prognosis of QNBC in comparison with TNBC.

Clinical peculiarities of QNBC

BC patients with negative androgen receptors and positive lymph nodes are at a relatively higher risk of relapse and death (with five-year disease-free survival of 51% and five-year overall survival of 60%) (Hu et al., 2017). The prognostic value of the androgen receptors is statistically significant in

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BC patients aged 40-60 years, with premenopausal status, large tumour size (2-5 cm), more lymph node involvement (four and more), high tumour stage (III), high differentiation grade (III), positive vascular invasion, positive p53, negative cytokeratin 5/6 (CK5/6) and higher Ki-67 proliferation index (50%-100%).

Among 400 consecutive invasive BC patients, there are 32 QNBCs (8% of the cases) (Safarpour et al., 2014). QNBC patients are at a mean age of 58 years (range, 29 to 84 years). Fourteen patients (43.75% of the cases) are aged at least 60 years. QNBCs are poorly differentiated and have the highest Ki67 proliferation index. Lower androgen receptor expression correlates with earlier metastasis, shorter disease-free intervals, and lower survival rates. Morphologically, four QNBCs are metaplastic/special type carcinomas with squamous or chondroid differentiation, three are moderately differentiated ductal carcinomas, and one is a poorly differentiated apocrine carcinoma as three of the remaining 24 poorly differentiated carcinomas have apocrine features. The poorly differentiated infiltrating carcinomas have high mitotic rates, variable lymphoplasmacytic infiltrate, and/or tumour cell necrosis. Three of the 24 poorly differentiated QNBCs have BRCA1 germline mutation and one QNBC has BRCA2 one. The median Ki67 proliferation index in 17 QNBCs is 64% (range, 18% to over 90%). Three apocrine carcinomas are with Ki67 proliferation index values of 18%, 22%, and 22%, respectively.

Within the population-based prospective Malmö Diet and Cancer Study in Sweden, among 516 invasive BCs, there are 49 androgen receptor-negative ones (9.50% of the cases) (Elebro et al., 2014). Androgen receptor negativity is significantly related to estrogen receptor and progesterone receptor negativity, higher tumour grade, and higher Ki67 proliferation index value. Cox regression analyses stratified by androgen receptor status indicate significant associations between reproductive factors and androgen receptor-negative BC. The older the woman at first childbirth, the higher the risk of androgen receptor-negative BC (p for trend=0.001)

Among a total of 333 BC patients, those with QNBC are statistically significantly younger (p=0.007) and with more seldom nodal involvement (29% versus 40%; p=0.040) when compared to androgen receptor-positive BC (Guiu et al., 2018). They exhibit tumours with statistically significantly higher differentiation grades (grade 1-2 only: 12.1% versus 32%; p<0.001) and more rare lobular histology (1.5% versus 8.9%; p=0.007), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations (3.3% versus 27.6%; p<0.001), more common basal-like phenotype (73% versus 53.6%; p<0.001), BRCA1 promoter methylation (35.9% versus 9.2%; p<0.001) and defects in phosphatase and tensin homolog (PTEN) (34.1% versus 15.3%; p=0.009). Patients with androgen receptor-positive/Forkhead box protein A1**(**FOXA1)-positive, androgen receptor-positive/FOXA1-negative, and androgen receptor-negative BCs show three-year recurrence-free survival rates of 79.8%, 79.1%, and 86.9%, respectively, and five-year recurrence-free survival rates of 66.8%, 79.1%, and 79.7%, respectively. Recurrence-free survival is statistically significantly shorter for androgen receptor-positive/FOXA1-positive tumours than for the other ones (androgen receptor-positive/FOXA1-negative and androgen receptor-negative) (p=0.020).

Biomarkers of QNBC

S-phase kinase-associated protein 2 expression inversely correlates with prognosis in invasive BC as well as with the expression of estrogen receptors and human epidermal growth factor receptor 2 (Yang et al., 2015). The transcription factor CEBPB, peroxisome proliferator-activated receptor delta, and thyroid hormone receptor-interacting protein 13 are identified as promising potential biomarkers for QNBC (Peluffo et al., 2019). The results from a recent study demonstrate that high thymidylate synthase concentrations correlate with worse prognosis and can be a valuable prognostic biomarker in QNBC patients (Siddiqui et al., 2019).

The investigation of the combined androgen receptor, E-cadherin, Ki67 proliferation index and CK5/6 expression in TNBC patients demonstrates that the absent androgen receptor expression is significantly associated with highly undifferentiated BCs (Adamo et al., 2017). The Kaplan-Meier curves indicate that patients with androgen receptor- and E-cadherin gene (CDH1)-negative expression and high Ki-67 levels have a significant correlation with poor outcomes.

Engrailed-1 expression is associated with unfavourable overall survival in QNBC patients (Bhattarai et al., 2020).

In a cohort of 197 stage, I-III TNBC cases with a mean clinical follow-up of 53.6 months, lack of androgen receptor expression correlates with the expression of cancer stem cell phenotype (CD44+/CD24-) (p<0.001), cyclooxygenase-2 **(**COX-2) (p=0.02), and two basal markers such as CK5 (p=0.03) and nestin (p=0.01) (Riaz et al., 2020). The basal-like phenotype (TN, CK5-positive, and/or nestin-positive) correlates with QNBC and demonstrates a statistically significant association with adverse prognostic markers such as high proliferation index (p<0.001), COX-2 expression (p=0.009) and cancer stem cell phenotype (CD44-positive/CD24-negative; p=0.01). Integration of immunohistochemical analysis of androgen receptors and basal biomarkers to the assessment of TNBC tumours can improve the prognostication of an otherwise heterogeneous disease.

The results from the retrospective cohort study of 912 BC females in Stockholm, Sweden, show a negative androgen receptor expression in 136 out of 770 examined patients (in 17,66% of the cases) (Hilborn et al., 2016). Within the TNBC

patients' subgroup, androgen receptor expression predicts a better disease-free survival rate following tamoxifen therapy (of 85.7% in positive androgen receptors versus 65.5% negative ones; log-rank p=0.0544) and overall survival rate (95.2% versus 76.2%; log-rank p=0.0355, respectively). Among the subgroup with a non-pathological complete response to tamoxifen, androgen receptor positivity selects a group with a statistically significantly better disease-free survival rate (p=0.045) and overall survival rate (p=0.021), however, not among the subgroup with the pathological complete response. The QNBC patients have worse outcomes and increased recurrence rates after tamoxifen therapy (hazard ratio of 3.98; between 1.32 and 12.03 at 95% confidence interval; p=0.014). In terms of BC-specific survival rate, these patients present with increased risk (hazard ratio of 3.97; between 1.12 and 14.10 at 95% confidence interval; p=0.033).

Micro ribonucleic acids in QNBC

Non-coding ribonucleic acids (RNAs) such as microRNAs, long non-coding RNAs, and circular RNAs play a significant role in BC tumourigenesis by virtue of their oncogenic and tumour-suppressive properties (Paul & Banerjee, 2022). The non-coding RNAs are important in tumour proliferation, progression, and metastasis in terms of their use as biomarkers for future diagnostic applications. They are explicitly implicated in BC regulation and their cross-talk between TNBC and QNBC is discussed.

The identification of QNBC-specific circulating microRNAs may improve tumour detection and prognosis (Bhattarai et al., 2020).

The assessment of androgen receptor mRNA expression in 925 BCs from the Cancer Genome Atlas and 136 BCs in two confirmation sets reveals that androgen receptor-negative African American patients are diagnosed at a younger age than androgen receptor-positive ones (Davis et al., 2018). The androgen receptor-negative patients have an odds ratio of 66.60 (between 32.86 and 146.06 at a 95% confidence interval) for being basal-like and this is associated with a longer time to progression and shorter overall survival. Age- and stage-adjusted QNBC patients have more basal-like tumours than TNBC ones (70.8% versus 3.2%). African American QNBC patients predominately demonstrate BL1, BL2, and IM subtypes, with differential expression of E2F1, NFKBIL2, CCL2, TGFB3, CEBPB, phosphoinositide-dependent protein kinase 1 (PDK1), IL12RB2, IL2RA and SOS1 genes than white patients. Immune checkpoint inhibitors programmed cell death 1 (PD-1), programmed cell death ligand-1 (PD-L1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) are statistically significantly upregulated in overall QNBC and African American QNBC patients as well. Functional pathways related to androgen receptor-negative status only include nuclear mRNA splicing via spliceosome and BM CD105-positive endothelial expression regulation. The androgen receptors can be used as a BC prognostic marker, particularly in African American QNBC patients.

Comparative assessment of TNBC and QNBC

The redefinition of QNBC that distinguishes this malignant neoplasm from TNBC by the androgen receptor absence can help identify patients with a relatively higher risk of disease relapse and death (Hu et al., 2017). The androgen receptor is emerging as a novel prognostic biomarker in TNBC (Yang et al., 2018). Loss of androgen receptor immunoexpression does not predict adverse clinical outcomes in TNBC patients (Zaborowski et al., 2019). The analysis of the correlation of the androgenic pathway with tumour cell proliferation in invasive ductal TNBCs demonstrates a higher incidence rate of distant metastases in the QNBCs (McNamara et al., 2013).

The prognostic role of the androgen receptors in TNBC is ambiguous (Bhattarai et al., 2020). Several studies associate loss of androgen receptor expression with worse prognosis in TNBC patients while others attribute worse outcomes to increased androgen receptor signaling (Bhattarai et al., 2020). The variations in results of different studies are due to differences in the patient populations and/or to variations in methodology (Safarpour et al., 2014).

Negative androgen receptor expression is established by immunohistochemistry in 83 of 121 TNBC patients (in 68.60% of the cases) (Sutton et al., 2012). The decreased intratumoural androgen receptor expression may be predictive of distantly metastatic TNBC.

The immunohistochemical investigation of a cohort of 492 TNBC patients in South Korea reveals lack of androgen receptor expression in 87 females (in 17.68% of the cases) (Choi et al., 2015).

Among 135 invasive TNBC patients immunostained for androgen receptors, a 1% cutpoint is confirmed as the appropriate threshold for androgen receptor positivity (Astvatsaturyan et al., 2018). Using this cutpoint, 80 or 59.26% of these TNBC cases are QNBC. The high-risk (negative androgen receptor and positive epidermal growth factor receptor expression) is the basal molecular subtype with the worst prognosis and may benefit the most from chemotherapy regimens. The intermediate-risk subtype (negative androgen receptor and negative epidermal growth factor receptor expression) presents with an intermediate prognosis. In metastatic QNBC samples, epidermal growth factor receptor expression is increased and this is related to poor outcomes.

A single study of the prevalence of androgen receptor expression in 88 patients with inflammatory BC demonstrates that 12 out of a total of 17 TNBCs are androgen receptor-

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negative (70,59% of the cases) (Gong et al., 2014). Female patients with QNBC present with statistically significantly inferior five-year survival rates than those with androgen receptor-positive TNBC and the other histological subgroups ($p<0.03$).

Similarly to TNBC, QNBC disproportionately impacts Black/African-American women and plays an important role in survival disparities experienced by these patients (Jinna et al., 2022). The racial disparities of QNBC and molecular signaling pathways that contribute to QNBC aggressive biology in Black/African-American females are discussed.

In 190 TNBC patients, the prognosis of androgen receptor-positive patients is statistically significantly better ($p=0.019$, log-rank) than that of androgen receptor-negative ones, i.e. of ONBC cases (Asano et al., 2017). In multivariate analysis, androgen receptor expression is an independent indicator of good prognosis (hazard ratio of 0.36; $p=0.039$). Since androgen receptor positivity statistically significantly correlates with better prognosis in patients with disease relapse ($p=0.034$, log-rank), the androgen receptor expression may be a useful subclassification prognostic marker in TNBC.

Within a retrospective investigation based on a tissue microarray, the comparison between 213 QNBC cases and 74 TNBC ones reveals a correlation of the androgen receptor status with patient's age, tumour size, stage, grade of disease, nodal status and type of treatment such as surgery, chemotherapy and radiotherapy (He et al., 2012). The frequency of positive lymph nodes is higher in QNBC than in TNCB patients. The results from the multivariate analyses prove that the disease-free survival and overall survival are statistically significantly shorter in QNBC than in TNCB cases thus indicating the prognostic value of androgen receptor expression in operable TNBC.

The immunohistochemical examination of the expression of androgen receptors, epidermal growth factor receptors, and basal markers such as CK14 and 34βE12 in 699 invasive TNBCs in tissue microarrays by means of the streptavidin-biotin method demonstrates immunohistochemical positivity in 38% of the cases only (Thike et al., 2014). Disease-free survival is statistically significantly better in androgen receptor-positive TNBC than in QNBC. Androgen receptor expression is inversely associated with tumour histological grade and mitotic score. Loss of androgen receptors in TNBCs including those with basal-like features augurs a worse patient's prognosis.

A statistically significantly better five-year disease-free survival rate is established in patients with androgen receptor-positive TNBC than in patients with QNBC ($p=0.002$) (Riaz et al., 2018). The examination of the expression of the androgen receptors and cancer stem cell markers such as positive CD44/negative CD24 and positive aldehyde dehydrogenase 1 (ALDH1) in invasive BC reveals that the concordant expression of positive androgen receptors and positive estrogen receptors in TNBC is associated with a statistically significantly better patient's outcome ($p<0.001$) when compared to concordantly negative androgen receptors and negative estrogen receptors in QNBC.

Among primary BC patients treated with neoadjuvant chemotherapy within the prospective GeparTrio phase-III trial, QNBC females present with poorer disease-free survival (65.5% versus 85.7%; log-rank $p=0.0544$) and overall survival (76.2% versus 95.2%; log-rank $p=0.0355$) than TNBC ones (Loibl et al., 2011).

The experiments with or without dihydrotestosterone treatment in three TNBC cell lines identify **the androgen receptor negatively induced long non-coding RNA (ARNILA),** which correlates with poor progression-free survival in TNBC patients and promotes epithelial-mesenchymal transition, invasion and metastasis *in vitro* and *in vivo* (Yang et al., 2018).

Conclusion

BC patients with negative androgen receptors and positive lymph nodes are at relatively higher risk of relapse and death. QNBC women present with poorer disease-free and overall survival than TNBC ones. The review of the recent literature reveals a greater paucity of prognostic biomarkers in QNBC patients than in TNBC ones. Microribonucleic acids play important roles in TNBC and QNBC proliferation, progression and metastasis and are used as biomarkers for future diagnostic applications. It is necessary to further intensify the problem-oriented interdisciplinary research in the field of prognostic biomarkers of QNBC.

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