

Triple-negative breast cancer: current state of the art

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ABSTRACT

Aims and background. Triple-negative breast cancer, defined by a lack of expression of estrogen, progesterone and HER-2 receptors, accounts for 15% of all types of breast cancer. The subtype mainly includes a molecularly distinct subgroup, the basal-like subtype (accounting for 75% of all cases). We attempt to define triple-negative breast cancer and compare it with basal-like disease, review the molecular, pathologic and clinical features of triple-negative disease, provide an overview of a retrospective subset analysis of clinical trials, and outline ongoing therapeutic trials and possible paths for future research.

Methods. We collected data regarding classification, molecular and clinical features and treatment, drawn from the existing literature, including abstracts and verbal accounts. By the term "basal-like", we defined all cases where gene expression array or more sophisticated immunophenotypes are used for identification. When the analysis is restricted to clinical assay (immunohistochemistry), we refer to "triple-negative".

Results. Basal-like breast cancer expresses genes characteristic of basal epithelial cells, which include high-molecular weight basal cytokeratins (CK5/6, CK14, CK17), vimentin, p-cadherin, alpha B crystalline, caveolins 1 and 2 and EGFR. The expression of basal markers (basal cytokeratins and EGFR) is related to a worse prognosis and identifies a clinically distinct subgroup within the triple-negative breast cancer. BRCA1 mutations are present in 11% of triple-negative tumors and even more rare is BRCA2 deficiency. BRCA1-associated breast cancers types are typically characterized by a high rate of DNA aberrations and defective DNA repair pathways (the so-called "BRCAness"). The use of regimens based on DNA-damaging agents, such as anthracyclines, platinum derivatives and cyclophosphamide seems a sensible option for this breast cancer subtypes. Clinical data support a strong sensitivity to primary chemotherapy with pathologic response rates ranging from 27-45% (with anthracyclines and taxanes) to more than 60% with platinum-based triplets. However, based on retrospective data, major response to chemotherapy does not carry better survival ("triple-negative paradox"). There is no specific targeted therapy in the armamentarium: ongoing trials include anti-angiogenic agents, anti-EGFR and EGFR-TK inhibitors, epothilones and PARP inhibitors.

Conclusions. A specific systemic regimen cannot yet be recommended. Moreover, only a few data are available on which treatment selection can be based. Use of the existing cytotoxic agents can be optimized for this patient subgroup by investigating the proliferative signals and the suitability of these signals as therapeutic targets, besides assessing the BRCA1-pathway in this subgroup as regards treatment. A greater understanding of the pathologic and molecular characteristics of this phenotype may lead to customized treatment for these patients. Free full text available at www.tumorionline.it

Key words: triple-negative breast cancer, basal-like breast cancer, BRCA1, platinum agents, PARP-inhibitors, EGFR-inhibitors, antiangiogenic drugs.

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