The Challenge of Triple Negative Breast Cancers

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The role of hormones (estrogen) in breast carcinogenesis was recognized even in the nineteenth century. About 70 % of breast cancers express estrogen receptors (ER), and ER positive tumors proliferate in response to estrogen. ER positive tumors had better prognosis compared to ER negative ones. Estrogen receptor negative tumors have recurrences twice as much as those with tumors containing ER, independent of other prognostic markers. Selective estrogen receptor modulators (SERM), tamoxifen and raloxifene respond only in ER positive tumors [1].

One of the most aggressive types of sporadic breast cancers is those which are over-expressing the gene, HER-2/neu. It has been identified that ~25 % of breast cancers are over-expressing the HER-2/neu gene. Cancers which over-express HER-2/neu genes are highly resistant to conventional therapies and also very aggressive in their biological characteristics, including local and distant metastasis.

The combination of the three markers, ER, progesterone receptor (PR) and HER-2/neu is very commonly used for assessing treatment plan and prognosis. Cancers which are negative for all three, the so-called triple negative breast cancers (TNBC), are very resistant to conventional treatment plans. One of the greatest challenges in contemporary clinical practice is the management of triple negative breast cancers.

Molecular phenotype of breast cancer is done on the basis of five markers, ER, PR, HER-2, CK 5/6 and EGFR. ER positive and/or PR positive and HER2 negative are classified as luminal A, ER positive and/or PR positive and

HER2 positive are luminal B cancers, ER and PR negative and HER2 positive are considered as HER2 type. ER, PR and HER2 negative and positive for CK 5/6 and/or EGFR are categorized as basal-like cancers (BLBC). Those cancers negative for all five markers are considered as “unclassified” or “null” [2].

TNBC shares morphological and genetic abnormalities with basal like breast cancer (BLBC), but they are not the same entity. Breast cancers which carry BRCA1 mutations also very often come under TNBC/BLBC. They frequently occur in younger women and are aggressive and metastatic. They relapse more often and have a worse prognosis. Approximately 10–24 % of breast cancers are TNBC. About 70 % of TNBC are BLBC. TNBC and BLBC share many common characteristics like grade 3 status, ductal carcinomas with high mitotic count, high apoptotic rate, geographic or central necrosis and/or fibrosis, a pushing border of invasion and stromal lymphocytic response. Hormone negativity, high grade, medullary-like histology, lymphocytic infiltration, TP53 mutations, EGFR expression, HER-2 negativity, characteristic copy number alterations and X—chromosome inactivation are termed as “BRCAness” because of their similarity to BRCA1 mutation carriers. Thus, there is considerable overlap between the three entities, namely, BLBC, TNBC and BRCA1 mutation carriers [3].

Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) are commonly used to measure these markers. IHC is a labor intensive method whereas FISH is expensive. To reduce the cost factor, there have been some reports of assessment of HER-2/neu by chromogenic in situ hybridization (CISH), which is cheaper. However, this method needs further standardization before it can be done in routine clinical practice.

We have previously done a study [4] where we have compared IHC and PCR for HER-2/neu assessment. It was

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done on a small population and we did not find a high concurrence (HER2/neu IHC+: 40 % vs. PCR 25 %). This probably could have been due to the fact that IHC 2+ cases were also included as positive and also because we have used very stringent cut-off points for quantitative PCR. In our study, 83 cases of TNBC out of a total of 358 cases, 23.2 % were detected (Unpublished data).

Du et al. have analyzed 294 breast cancer patients for ER, PR and Her-2/neu by quantitative RT-PCR and they suggest that this would be a better method for sub-typing breast cancer and predicting the prognosis [5]. Denkert et al. also suggest that RT-PCR could be used for hormone receptor studies (ESR and HER-2/neu). They studied 1050 patients by RT-PCR for ESR-1 and HER2 and found good correlation with IHC [6]. Bastien et al. studied 814 breast cancer patients and recommend that RT-qPCR is a better way to study ESR1 and HER-2 than IHC [7].

PCR would be a useful diagnostic tool for assessing HER-2/neu, but it is as yet not popular. PCR would give fast results (compared to IHC, which can take a full day to complete the procedure). PCR results can be quantified (compared to IHC results which are subjective to a certain extent, especially the difference between IHC 2+ and IHC 3+). PCR can also be used as a cost effective method, compared to FISH which is expensive. Again PCR can be done as a quantitative assay whereas IHC is more subjective. Thus, once standardized PCR can be used as a very useful alternative to other methods and could be employed for diagnosis of TNBC.

There is also an additional need for developing novel markers for the early diagnosis of TNBC. A recent publication has identified 11-protein signature for lymph node negative triple negative breast cancer [8]. The current modality of chemotherapy for TNBC is neo-adjuvant therapy, which over-treats many patients. The treatment is

also highly cytotoxic. Identifying novel markers via proteomic techniques could help in sub-typing TNBC and hence have tremendous clinical applications. Novel drugs could also be developed against these potential markers.

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