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TRIPLE NEGATIVE BREAST CANCER: A MOLECULAR SKETCH

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ABSTRACT

Triple-negative breast cancer, portrayed by cancers that don't express estrogen receptor (ER), progesterone receptor (PR), or HER-2 gene, represents an essential clinical challenge in light of the fact that these cancer don't react to endocrine treatment or other accessible targeted agents. The metastatic potential in triple-negative breast cancer is like that of other breast cancer subtypes, yet these cancers are connected with a shorter middle time to backslide and demise. One vital objective is thusly the identification of prognostic elements and markers to dependably select high and low risk subsets of patients with triple-negative cancer for distinctive treatment methodologies of subtypes with differential responsiveness to particular agents. However, a solid prognostic marker has been subtle, and markers have been conflictingly valuable. For instance, epidermal growth factor receptor (EGFR) have been investigated, yet there is still an absence of concession to a standard measure or cutoff for EGFR expression levels regarding prognosis. Correspondingly, in light of the fact that triple-negative status is basically utilized as a surrogate for basal-like breast cancer, particular basal markers have been investigated. Chemotherapy remains the backbone of treatment for triple-negative breast cancer, however imperative impediments still should be overcome in the following couple of years if any noteworthy clinical steps are to be made.

KEYWORDS: Chemotherapy, triple-negative breast cancer, HER2, basal-like breast cancer.

INTRODUCTION

Breast cancers are very heterogeneous and may show diverse gene of hormone receptors.[1] estrogen receptor, progesterone receptor and human epidermal cancer factor receptor 2

(HER2) status.[2] and together this data serves to recognize distinctive sorts of breast cancers: luminal A (HR+/HER2−, which is a cancer grade 1 or 2), luminal B/HER2− (HR+/HER2−, which is a cancer grade 3 or 4), luminal B/HER2+ (HR+/HER2+), triple negative (HR−/HER2−), or HER2 overexpressing (HR−/HER2+).[3] Together luminal A and B subtypes represent 65%–70% of all breast cancers, though 10%–15% are triple negative and 10%–20% are HER2 overexpressing.

Gene expression investigation has distinguished molecular classes of breast cancer that are clinically and biologically discrete.[4] One of these subgroups, which has pulled in noteworthy consideration recently, is basal-like breast cancer. BLBC is portrayed by articulation of gene generally found in basal/ myoepithelial cells of the ordinary breast. BLBC are set inside a cluster of estrogen receptor and HER-2-negative cancers and are connected with poor prognosis. In spite of the fact that gene expression profiling is viewed as the "gold standard" technique for distinguishing proof of BLBC, this methodology is not at present feasible for extensive scale clinical applications or review studies utilizing formalin fixed, paraffin-embedded samples.[5-7] Breast cancer is divided into four groups (Table 1), as indicated by their gene expression profiles (GEP). These are: luminal A, luminal B, human epidermal cancer factor receptor 2 (HER2) amplification, and basal-like. Triple negative breast cancer (TNBC) is a subtype of breast cancer that imparts to the basal-like group.[8]

Table 1. Breast Cancer Classification based on Gene Expression Profile

Classes	ER	PR	HER2	Grade	Prognosis
Luminal A	Positive	Positive	Negative	Low	Good
Luminal B	Positive/Negative	Positive/Negative	Positive/Negative	High /Intermediate	intermediate
HER2	Negative	Negative	Positive	High	Poor
Basal-like	Negative	Negative	Negative	high	Poor

Expression of basal/myoepithelial cell proteins recognized by immune-histochemical recoloring has been utilized as a surrogate of gene expression.[9-10] On the other hand, there is right now no accord on the ideal immune-histochemical board to characterize BLBC and a few mixes of basal markers. In light of the successive expression of basal cytokeratins in BLBC and the relationship between basal cytokeratins and poor guess, a few studies, including our own, have utilized basal cytokeratins (i.e. CK5/6, CK17, and CK14) alone to characterize BLBC regardless of the expression of different markers.[11] The implication of ER-positive/basal cytokeratin positive cancers is still unknown, and the majority of the BLBC distinguished by gene expression are described by ER and HER-2 negativity (figure-

1). Hence, it has been alleged that it is more biologically acceptable to confine identification of BLBC to inside of the ER-and HER-2-negative group of cancer.[12-14]

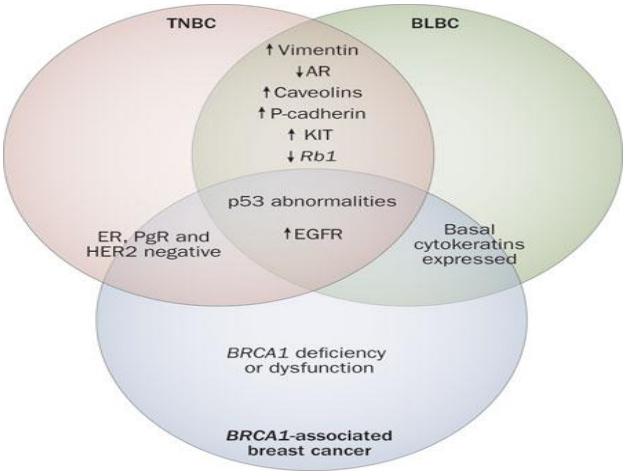

Figure 1: Gene expressions of TNBC

Molecular subtypes of TNBC

Triple-negative cancer envelops various molecular subtype (Figure 2). The real segments of triple-negative cancers are the basal-like and, a recently identified claudin-low molecular subtypes.[13] Basal-like breast cancer have a few molecular features. These incorporate low signals for the ER-related gene cluster and the HER-2–related gene cluster. Thus, these cancers generally are negative for ER, PR, and HER-2 on clinical examines.[14-15] Basal-like cancers express proliferated genes and a unique bunch of gene, known as the basal cluster, which incorporates basal cytokeratins and epidermal cancer factor receptor (EGFR). They are regularly p53 mutant and have confirmation of genomic instability, which may be therapeutically pertinent.[16] It is turning out to be clear that the triple-negative phenotype on clinical examines enhances for basal-like cancer, however there is harshness between these two groups. Around 25% of triple-negative breast cancers are not basal-like on gene expression cluster.[17-20]

Likewise, there are basal-like breast cancer which are not triple-negative, but additionally signify around 25% of cases. Subsequently, in clinical studies taking a gander at basal biology and utilizing the triple-negative phenotype to distinguish patients.[21-22]

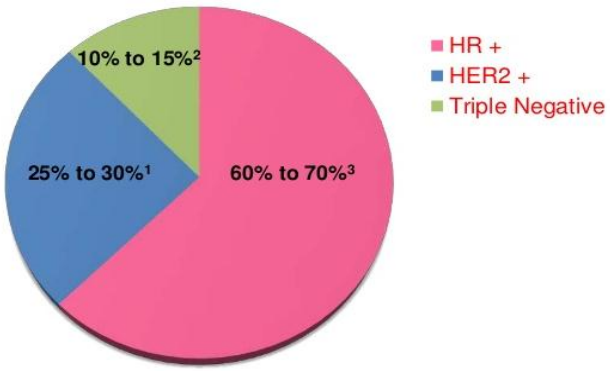

Figure 2: current clinical subtypes of breast cancer

These particular types of breast cancers all have distinctive characteristics, prognosis and furthermore react contrastingly to drug treatments. About seventy five percent of all breast cancer are ER+ and are dependent on estrogen for cancer development, giving a useful target to treating these cancers by means of ER modulators or down regulator or aromatase inhibitors. Just 20%–40% of patients with advanced ER+ breast cancer have a reaction to endocrine treatment, which only averages to 8 to 14 months.[23-25] Luminal A type tend to have the best result with a 95% 5-year survival rate, while luminal B cancers, which tend to have lower HR expression and in this manner less sensitivity to endocrine treatment yet increased sensitive to chemotherapy, tend to have a more regrettable result. Ordinarily found in younger patients, triple-negative breast cancers (TNBCs) are associated with germ line BRCA transformations. TNBCs likewise have higher relapse rates and diminished patient survival than other breast cancer type.[26] HER2-overexpressing breast cancers likewise have poor prognosis and high metastases rates, and as they need HR expression, they don't react to endocrine treatments and are resistance to current chemotherapies. These breast cancer types can be further divided into a large number of subtypes, and these subtypes show particular gene mutation that have yet to be completely characterized.[27]

Currents Status of TNBC Therapeutics

Known hereditary factor like acquired BRCA mutations give a lifetime risk of developing breast cancer of 60% to 85%, however, these mutation represent just 2%–3% of all breast cancer cases. Spontaneous mutation in PIK3CA are a significantly more common in breast cancer.[28] While PIK3CA mutation have been shown to be connected with enhanced patient diagnosis, these hereditary variation have additionally been shown to impart resistance to trastuzumab, a typical treatment choice for HER2-overexpressing breast cancer. Recognizing gene mutation in patients with TNBC is particularly critical in light of the fact that these

cancers currently don't have direct target for medications.[29] Hence, it is critical to study both the immunohistochemical properties and hereditary profile of every breast cancer to optimize treatment regimens and avoid superfluous medication toxicities and ultimately enhancing patient outcomes.

Current treatment methods for triple-negative cancer incorporate anthracyclines, taxane, ixabepilone, platinum agents.[30] Recently, EGFR inhibition has been proposed as a therapeutic mechanism in triple-negative breast cancer. Agents that target poly (ADP-ribose) polymerase and androgen receptors have additionally been proposed in these patients. Triple-negative breast cancer is unmistakably a particular clinical subtype, from the viewpoint of both ER and HER-2 expression, yet further sub classification is required. At present, there is not a single agent that target in triple-negative breast cancer.[31]

There are various diverse next generation sequencing (NGS) platforms available, but these are very costly both in instrument and test cost, and in this manner, these apparatuses are farfetched for far widespread clinical use.[32] However, new innovation like the Ion Torrent sequencing platform has been appeared to be more cost and time effective with solid results, which may help make cancer DNA sequencing and customized medications a reality for every cancer patient in the near future.[33]

Closing Remarks

TNBC is an exceptionally aggressive and metastatic cancer with an extremely poor anticipation with a present five-year survival rate of under 30%. Since the present therapeutic treatment for TNBC have just restricted efficacy, elective treatments are desperately expected to enhance the prognosis for TNBC patients. This survey concentrates on the capability of nanoparticles as successful enhancers of treatment for TNBC cancers. In spite of the promise of targeted therapies, cytotoxic chemotherapy remains the pillar of treatment for patients with TNBC. This is risky not just as a result of the various toxicities of cytotoxic chemotherapy but additionally also have high recurrence rates and the survival of patients who have metastatic cancer stays terrible. The distinguishing proof of molecular subtypes is the key for comprehension of the biological attributes of TNBC for developing customized medications.

Triple-negative breast cancer is additionally a surrogate of basal-like breast cancer. hence, trials intended to accumulate patients with basal-like breast cancer utilizing ER/PR and HER-2 negativity give a guess of the triple-negative population, there is some conflict, including

some HER-2 positives and some ER positives among the basal. At present, there is not a single successful and effective agent that target a driving vulnerability in triple-negative breast cancer. On the other hand, there are various potential treatments currently under scrutiny that may in the long run enhance results in these patients.

Conflicts of Interest Statement: The Authors declare no conflicts of interest.

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