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Review

From molecular insight to therapeutic strategy: The holistic approach for treating triple negative breast cancer

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ABSTRACT

Aim of the present study was to analyze the molecular pathogenesis of TNBC, therapeutic practice, challenges, and future goals in treatment strategies. Based on the alterations of distinct pathways, Lehmann's subgroups of TNBCs were further categorized. Those with defective DNA damage repair and replication pathways, viz. Basal Like 1 & 2 (BL1, BL2) were found susceptible to DNA intercalating drugs while those with upregulated cell signalling & motility (mesenchymal (M), mesemchymal stem like (MSL)), cell survival (BL2, M, MSL), angiogenesis (BL2, MSL), T cell signalling (Immunomodulatory/IM) pathways required targeted therapies. Our Meta-analysis categorized 12 randomized previous trial cases, solely under the following drug regimens: [1] DNA destabilizers, [2] PARP inhibitors, [3] Microtubule stabilizers, [4] Angiogenesis inhibitors, [5] Antimetabolite, [6] T cell targeted therapy; as single or combinational therapy.

Best therapeutic efficacies of DNA destabilizers with angiogenesis inhibitors in combination than monotherapy with either (OR: 5.011-7.286; p value < 0.001) indicated a significant prevalence of BL1 type TNBCs in populations. Statistical significance with antimetabolites as combination therapy (OR: 2.343; p value: 0.018) and not with microtubule stabilizer (OR: 0.377) were observed.

Thus, for best ORR in TNBC, personalized medicine should be the therapeutic choice for the clinicians.

Contents

Abbreviations: BC, breast cancer; LAR, Luminal Androgen receptor; BL1, Basal Like 1; BL2, Basal Like 2; MSL, Mesenchymal Stem-Like; M, mesenchymal; IM, immunomodulatory; UNS, unstable; HR, homologous recombination; pCR, pathologic complete response; ORR, Objective Response Rate.

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1. Introduction

Triple Negative breast cancer [TNBC], the most heterogeneous and a major aggressive form of breast cancer, accounting for 10–17% of all diagnosed cases of BC [1], represent an important clinical challenge owing to their high metastatic potential and recalcitrance to endocrine therapy or other available targeted agents [1,2]. TNBC has remained a matter of major concern and extensive research worldwide [3,4]. Compounding universal risk factors of TNBC include younger age, waist/hip ratio, breastfeeding history, parity, genetic predisposition and ethnicity [5].

Owing to their distinct molecular heterogeneity, treatment algorithm of TNBC warrants an in depth understanding of their classification. Thus, the present study is aimed at understanding the necessity of specific therapeutic regimen, based on the spectra of genetic alterations associated with different subgroups of TNBC.

2. Old school of classification of TNBC

The earlier system of classification of TNBC into subgroups viz Molecular Apocrine, Claudine Low and Basal like [6], relied purely on their stages of differentiation and expression of specific surface markers. The Molecular Apocrine subgroups of TNBC, the most differentiated amongst all subtypes, found mostly in advanced ages, account for 0.5%–4% of TNBCs with characteristic ER-, PR-, HER2- and AR+ signature [6]. The Basal Like subgroups manifest basal or myoepithelial cell like properties and account for 75% of all TNBC types [7]. Besides having the molecular signatures of Cytokeratin 5/6, 14, 17, basal like subgroups lack DNA repair and tumor suppressor genes attributed to locus 5q11 and have overexpression of *EGFR* [6]. The Claudine low subgroups which comprise of poorly differentiated proliferating mesenchymal stems cells [8], have characteristic CD44+/CD24- stem cell signature [6], upregulated signature of mesenchymal markers like *Slug*, *Twist* and *Snail* genes with potential role in tumor recurrence [6,9] are associated with worst patient outcome.

The uniqueness of TNBC subgroups lies not merely on their stages of differentiation or on the cellular origin but also on a spectrum of distinct genetic pathways up regulated in tandem with each of its subgroups. Based on such alterations, Lehmann et al. [10] redefined TNBC subgroups into distinct seven subgroups.

3. Molecular pathways altered in TNBC

A refined taxonomy of Lehmann et al. [10] described TNBC into seven distinct classes viz LAR (Luminal Androgen receptor), BL1 (Basal Like 1), BL2 (Basal Like 2), MSL (Mesenchymal Stem-Like), M (Mesenchymal) and IM (Immunomodulatory) based on alterations of distinct pathways amongst each subgroup. A distinct notion about the pathways altered in TNBC and the attributed phenotype conferred to each of these subgroups could provide novel insights into the pathogenesis and classification of the disease, driving forward molecular analyses to discover new treatments. Intense investigations are currently underway to study the underlying molecular pathways that drive the growth and dissemination of these tumours and to develop effective targeted therapies against them. Some of these pathways are discussed below.

3.1. Alterations of the DNA damage repair and cell cycle checkpoint pathways in TNBC

It has been observed that three quarters of BRCA1-associated tumors are BLBCs viz BL1 (Basal Like 1), the BL2 (Basal Like 2) and often the UNS (Unstable) subtypes which frequently show aberrant DNA damage repair pathway and cell cycle checkpoint [10,11]. The identification of such a deficiency in Basal-like tumor subtypes has important clinical relevance because DNA damage repair pathway impairment is the basis for specific target treatments. In addition, upregulation of genes associated with cell proliferation, such as *AURKA*, *AURKB*, *CENPA*, *CENPF*, *BUB1*, *TTK*, *CCNA2* etc. [10] have also been reported in the BL1 and BL2 subtypes. Owing to defects in homologous recombination (HR) pathway or cell cycle checkpoints as well as mutation of p53, BL1 subgroup show best pCR (pathologic complete response) compared to other subgroups [10,11] (Table 1, Fig. 1). Elevated expression of PARP (Poly ADP Ribose Polymerase) in BRCA1 mutant types is another important hallmark of identification of these tumors [11]. Replication inhibitors like Cisplatin, 5FU; PARP inhibitors viz Olaparib, Veliparib would confer better pCR for subgroups with these alterations [10] (Table 1).

3.2. Upregulation of cell signalling and cell motility pathways in TNBC

Upregulated expression of components of cell motility pathways has been found in more aggressive type of TNBCs like MSL (Mesenchymal Like) and M (Mesenchymal) type TNBCs (formerly Claudine Low) [6,10] (Table 1, Fig. 1). These include the components associated with EMT (Epithelial to Mesenchymal Transition) viz ECM-receptor interaction, ALK, Wnt/β-Catenin, and Rho-RacGTPases, the nonreceptor tyrosine kinase Src [10]. However, TNBC with upregulated signature of EMT (M and MSL type), show remarkably reduced expression of replication and cell cycle regulatory genes [10]. Microtubule stabilizing agents viz Ixabepi-

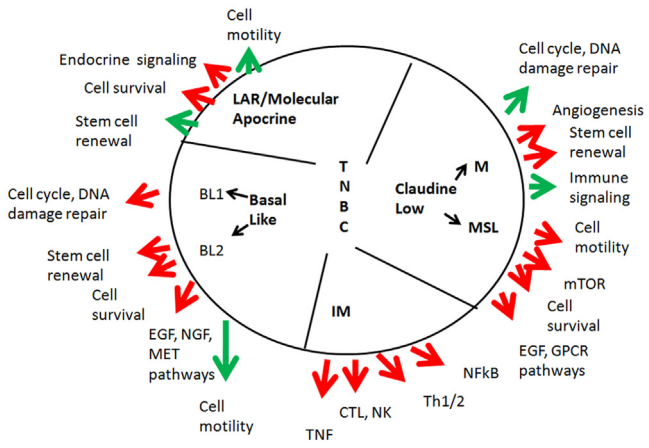

Fig. 1. The Different Subgroups of TNBC and the Associated Pathways. Red Arrow: Pathways Upregulated; Green Arrow: Pathways Downregulated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)