



TRIPLE NEGATIVE BREAST CANCER- AN OVERVIEW AND REVIEW OF LITERATURE

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Amit Gupta¹, Jyotika Jain², Ajay Kumar³, Sunil Kumar⁴, Neelam Wadhwa⁵, 1.3.4. Dept. of Surgery 5. Dept of Pathology, University College of Medical Sciences & associated Guru Teg Bahadur Hospital 2. Delhi State Cancer Institute,

ABSTRACT

CORRESPONDENCE:

Dr. Amit Gupta,
B1,503, Olive County,GH-9
Sector-5 ,Vasundhara
Ghaziabad PIN Code 201012
(U.P) INDIA
Email:
dramit2411@yahoo.co.in
Mobile No: (91)-9891981331

Triple-negative breast cancer refers to a specific subtype of breast cancer that does not express the genes for estrogen receptor (ER), progesterone receptor (PR) or Her2/neu. About 12-17 % of ca breast have triple negative ca breast This subtype of breast cancer is clinically characterized as more aggressive and less responsive to standard treatment and associated with overall poorer prognosis. Chemotherapy is the choice of systemic therapy for triple-negative tumors. They are more susceptible to non-receptor mediated therapies than other tumors.A numbers of new strategies are currently being tested in clinical trials.

Key Words: breast cancer, triple-negative, estrogen receptor (ER), progesterone receptor (PR), Her2/neu receptor

“Triple-negative entity represents a subtype of breast tumors with unique molecular and clinical characteristics, more aggressive and less responsive to standard treatment. In this scenario the molecular biology of this entity needs consideration.”

INTRODUCTION

Triple-negative breast cancer account for approximately 15% of all breast cancer cases. It refers to a specific subtype of breast cancer that does not express the genes for estrogen receptor (ER), progesterone receptor (PR) or Her2/neu receptor. This subtype of breast cancer is clinically characterized as more aggressive and less responsive to standard treatment and associated poorer overall patient prognosis. It is diagnosed more frequently in younger women, women with BRCA1 mutations, and women who belong to African-American and Hispanic ethnic groups.¹ We have witnessed more number of patients with Triple-negative breast cancer so an extensive review of literature regarding triple negative breast cancer was carried out through published literature and that culminated into this article.

Triple-negative breast cancers are generally unresponsive to standard receptor-mediated treatments. However, other forms of chemotherapy can still generate positive outcomes. Some reports even suggest they are more susceptible to non-receptor mediated therapies than other tumors. Although triple-negative breast cancer can be treated with chemotherapy, early relapse²⁻⁶ is common and a predilection for visceral metastasis is seen. If we see the survival curve in these patients there is a sharp decline in first 3rd to 5th year. Distant metastasis are much less common after 5 years. As presented in the comprehensive article by Drs. Anders and Carey, a number of studies have focused on understanding the epidemiology, natural history, biology,⁷ and treatment strategies for this subtype.⁸ Long-term follow-up of triple-negative cohorts has demonstrated a worse prognosis⁹ or the triple-negative subgroups than for those that are HR-positive. A number of new strategies are currently being tested in clinical trials.

Pathology

Triple-negative breast cancers refers to a specific subtype of breast cancer that does not express the genes for estrogen receptor (ER), progesterone receptor (PR) or Her2/neu. Biologically five distinct breast cancer tumor subsets are-

- hormone receptor (HR)-positive luminal A
- hormone receptor (HR)-positive luminal B
- human epidermal growth receptor 2 (HER2 positive)
- normal-like
- basal-like

Majority of triple-negative breast cancers carry the "basal-like"^{10,11} molecular profile on gene expression arrays. Although most triple-negative breast tumors do cluster within the basal-like subgroup, these terms are not synonymous; there is up to 30% discordance between the two groups. Triple negative is a term based on clinical assay and basal type is molecular phenotype defined using DNA microarray assay. Basal epithelial cell markers have higher expression of CK5,CK14,CK17,Smooth muscle marker,P53,P-cadherin,HER1/EGFR and lower expression of ER,PR,HER2,Desmin whereas luminal epithelial cell markers have higher expression of ER,PR,GATA3, Ck3, Ck8, Ck18, Ck19, Epithelial cell adhesion molecules, Alpha 6 integrin and lower expression of HER2,Basal Ck5,Ck14,Ck17. HER1/EGFR is expressed in approximately 60% of basal-like breast tumors. c-Kit expression is higher in basal-like tumors(31%). High p53 IHC expression or p53 gene mutations are common in basal-like breast cancer (82%). Several additional and targetable molecular pathways implicated in the pathogenesis of basal-like breast cancer include the mitogen-activated protein (MAP) kinase pathway, the Akt pathway, and the poly ADP-ribose polymerase 1 (PARP1) pathway. It has been observed that the majority of BRCA1-associated breast cancers are triple-negative and express a high proportion of basal-like cytokeratins (CK5, 14,

basal-like cytokeratins (CK5, 14, 17), as well as P-cadherin and HER1/EGFR. As BRCA1 is in part responsible for DNA repair, exploitation of this essential pathway holds therapeutic implications. Majority of triple-negative breast carcinomas are ductal in origin, others being metaplastic, atypical or typical medullary, and adenoid cystic. Clinical characteristics¹² of triple-negative breast cancers are onset at a younger age, higher mean tumor size, higher-grade tumors, higher rate of node positivity, more aggressive, less responsive to standard treatment, associated poorer overall patient prognosis. Visceral and soft-tissue relapse are more common.

Management

Because of the absence of specific treatment guidelines for this subgroup, triple-negative breast cancers are managed with standard treatment; however, such treatment leaves them associated with a high rate of local and systemic relapse. Triple-negative breast cancer cells do not express estrogen receptor (ER), progesterone receptor (PR) or Her2/neu receptors. Without these receptors, the cancer growth is not likely to be fueled by estrogen or progesterone, or by growth signals coming from the HER2 protein. Therefore, triple-negative breast cancer does not respond to hormonal therapy (such as tamoxifen or aromatase inhibitors) or therapies that target HER2 receptors, such as Trastuzumab. There is no standard recommendation that people with triple-negative breast cancer should routinely have more treatment. Research suggests that triple negative breast cancer responds better to chemotherapy than other types of breast cancer^{13, 14}. Although triple-negative breast cancer is associated with a generally poor breast cancer-specific outcome, it is not resistant to chemotherapy. They are more susceptible to non-receptor mediated therapies than other tumors. Triple-negative breast cancer is highly responsive to primary anthracycline and anthracycline /taxane

chemotherapy. In a retrospective analysis CMF is suggested to be superior to anthracycline based chemotherapy in basal like breast cancer¹⁵. While in a meta-analysis in triple negative patients anthracycline containing regimen was found to be superior to CMF¹⁶. BRCA1 dysfunction harboring deficient double-stranded DNA break repair mechanisms are sensitive to agents that cause DNA damage, such as platinum agents (cisplatin and carboplatin)¹⁷⁻²⁰. Few studies have shown that patients who have responded well to initial neo adjuvant chemotherapy have better outcome than non responders .it has been seen that % of responders is much less of in triple negative patients majority of them remain with residual disease. The newest chemotherapeutic agent available for treatment of metastatic breast cancer is ixabepilone,²¹ an epothilone analog. Epothilones bind tubulin, leading to stabilization of microtubules, cell cycle arrest, and subsequent apoptotic cell death.. In a group of 187 patients with triple-negative disease, response rate (RR) increased from 9% to 27% ^{with} the addition of ixabepilone to the capecitabine therapy, and progression-free survival (PFS) improved from 2.1 to 4.1 months.

EGFR expression is seen in approximately 60% of triple-negative breast tumors, thus providing a rational, targeted treatment approach. Cetuximab a chimeric monoclonal antibody targeting EGFR²²⁻²⁴.

The antiangiogenic agent bevacizumab ,a monoclonal antibody targets all forms of vascular endothelial growth factor (VEGF)- Histologic examination of "basal-like" triple-negative tumors has demonstrated the presence of glomeruloid microvascular proliferation. These focal endothelial tufts, which portend a worse prognosis in node-positive breast cancer may serve as targets for angiogenesis inhibitor therapy. PARP1, a gene that

encodes a chromatin-associated enzyme that modifies various nuclear proteins, is involved in the molecular events leading to cell recovery from DNA damage, cells deficient in either BRCA1 or BRCA2 are exquisitely sensitive to PARP1 inhibition, resulting in cell death/apoptosis. Several PARP1 inhibitors are currently in clinical development. Other emerging targets for treatment incorporate components of cellular proliferative pathways, including the phosphoinositide 3-OH kinase pathway and the mitogen-activated protein kinase pathway, DNA repair and c-kit.

CONCLUSION

Triple-negative breast cancer largely represents a subtype of breast tumors with unique molecular and clinical characteristics, distinctive risk factors and patterns of recurrence, association with BRCA1 mutation status, inferior prognosis, and expanding therapeutic options.

Multiple excellent approaches to improved care of triple-negative breast cancer, including DNA-damaging agents such as platinum²⁵, targeted agents against EGFR and VEGF, and PARP inhibitors are under investigation.

Current research strategies are aimed at better understanding both the risk factors and the biology underlying triple-negative breast cancer, with the goal of developing preventive measures and improving treatment strategies for this challenging subtype of breast cancer.

Conflict of Interest: Nil

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