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A Review of Triple-Negative Breast Cancer and Systemic Treatment

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Abstract: ***Triple-negative breast cancer (TNBC) is a heterogeneous disease that does not express the estrogen/progesterone-receptor (ER/PR), and human epidermal growth factor receptor-2 (HER2). TNBC is 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. This review describes the most recent data on targeted therapies that have demonstrated efficacy in the management of TNBC. The monotherapy will be efficacious in all patients with TNBC. The most effective treatment approach for these patients is likely to be a combination of targeted therapies with cytotoxic agents. Identification of molecular targets and tailored treatments based on the molecular alterations in individual cancers hold the best promise for improving the outcomes of this aggressive breast cancer.***

Keywords: Triple Negative Breast Cancer, BRCA Mutations, Targeted Therapies

1. Introduction

Breast cancer is the second most common cancer in the world and the most common cancer among women(Beiki et al., 2012). Breast cancer is a complex and heterogeneous disease with respect to histology, cellular origin, mutations, metastatic potential, disease progression, therapeutic response, and clinical outcome. It is the second leading cause of cancer death in women. Worldwide, it is estimated that more than 1 million women are diagnosed with breast cancer annually and that more than 410,000 will die of the disease **(Coughlin SS, et al 2009)**. Patients with breast cancer present with a wide range of clinical, pathologic, and molecular characteristics. Different forms of the disease vary with regard to clinical behavior, management options, and prognosis.

Triple-negative breast cancer (TNBC)

Triple Negative Breast Cancers" (TNBC) are comprised of heterogeneous breast cancers, defined broadly as breast cancers that lack protein expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal factor receptor 2 (HER2). Women who are young or of African-American descent are predominately affected by TNBC. There usually are high histological grades, high proliferation indexes, and more advanced stages at diagnosis (**Reis-Filho, et al 2008 &Maegaw, et al 2010**). TNBC is responsible for 10-15% of all breast cancer cases in women. [***C.K. Anders, et al 2009***]. According to epidemiological studies, the prevalence of TNBC varies greatly with ethic differences, being as high as 82% in Danish women, 39% in Arabic women, 19.3% in Chinese women, and 15.9% in Taiwanese women [***Kurian et al 2010, Tamimi et al 2009, Lin et al 2009, Lin et al 2009]***.A comparative study conducted in United States revealed a higher frequency of hormone receptor negative breast cancers in Asian women compared to Caucasians [***Kakarala M, et al 2010***].

TNBC &Genetic Counseling

Breast Cancer genetic counseling is a way of assessing your genetic risk of certain diseases, most commonly breast, ovarian, and colon cancer. A genetics evaluation can help an individual determine whether she has inherited an increased risk for cancer. Approximately 5 to 10 percent of all cancers are hereditary.Decisions about genetic testing are complex, and genetic counseling provides individualized information about the need for testing and the implications of testing. NCCN guidelines recommend that women ≤60 years with triple-negative breast cancer (TNBC) be referred for consideration of genetic counseling.

Connection between BRCA Mutations and TNBC

Women with triple negative breast cancer have a higher chance of having a BRCA mutation. Approximately 20% of women with triple-negative breast cancer are carriers of a BRCA1 or BRCA2 gene mutation. Interestingly, DNA microarray and immunohistochemical analyses revealed that 80-90% of breast cancers in women with germ-line mutations in BRCA1 are triple-negative (***Turner et al 2007***). Women with TNBC are approximately 5.6 times more likely to have BRCA1 mutation compared with non-TNBC. BRCA mutations greatly impact treatment decisions, considering that some treatment options are more effective for those with triple negative breast cancers, especially those with the BRCA mutation. TNBC and BRCA1 mutation were independently associated with younger age at diagnosis, as well as higher grade and stage tumors when compared with non-TNBC (***Mavaddat N, et al 2012***). In some triple negative tumors of high histologic grade, brca1 protein levels have been shown to be significantly lower, suggesting that the brca1 pathway may be dysfunctional in these tumor cells. Other mechanisms resulting in downregulation of BRCA1/2, including epigenetic alterations and overexpression of BRCA1 inhibitors are also associated with TNBC. Identification of the BRCA1 mutation among patients with breast cancer has been used as a prognostic factor and as a tool for treatment selection

Current Treatment Options & Potential Targeted Therapies in TNBC

TNBC is the only major type of breast cancer for which no specific FDA-approved targeted therapy is available to improve patient outcomes. Patients with triple-negative breast cancer do not benefit from hormonal or trastuzumab-based therapy. Early-stage TNBC is treated with a combination of surgery, radiation, and neoadjuvant/adjuvant chemotherapy, which can often lead to a good prognosis. Because of a current lack of targets for triple-negative disease, the main course of treatment is chemotherapy. Selection of chemotherapy is based on the traditional parameters used for breast cancer. Chemotherapy has obviously been the plinth of systemic treatment for TNBC. Molecular processes and biological drivers that have been targeted in TNBC include vascular endothelial growth factor (VGEF), inefficient DNA repair mechanisms (ie, PARP), the epidermal growth factor (EGFR, also called HER-1), mammalian target of rapamycin (mTOR). In general, clinical introduction of these molecules is hampered by a lack of predictive biomarkers. TNBC are being investigated as potential targets for therapy, some of which are summarized in Table 1.

Table 1: Triple-negative breast cancer (TNBC) Treatment Options

Treatment	Target	Chemo Drugs
Antibody Therapy	EGFR	Cetexumab
Antiangiogeneisis Antibody Therapy	VGEFR	Bevacizumab
Small Molecule Inhibitors of VEGFR	VGEFR	Sunitinib
PARP1 Inhibition	PARP1	BSI201
Cytotoxic Chemotherapy	DNA	Platinum Agents
Second Messenger Inhibition	mTOR	Everolimus

EGFR = epidermal growth factor receptor, VEGF = vascular endothelial growth factor
VEGFR = vascular endothelial growth factor receptor,
PARP1 = poly (ADP-ribose) polymerase-1
mTOR = mammalian target of rapamycin

EGFR (epidermal growth factor receptor)-targeted therapies

EGFR is known to be overexpressed in TNBC (*Gluz., et al 2009*).Approximately 66% of breast cancer patients with triple-negative tumour cells and basal-like tumour cells have been reported to express EGFR (*Rakha, et al 2007*). The epidermal growth factor receptor (EGFR) may be a potential target in the treatment of advanced TNBC. Cetuximab, a monoclonal antibody that targets EGFR, have shown somewhat limited benefit. Baselga, et al 2010 reported that, EGFR is an important target in TNBC, author reported that adding cetuximab to cisplatin doubled the progression-free survival duration from 1.5 to 3.7 months (HR 0.675, P = 0.032). The rate of response (RR) to cetuximab monotherapy was low at 6%. The RR to combination therapy with carboplatin at progression was 16%, while the RR to the combination at initiation of treatment was 17%. Overall, combination therapy with carboplatin/cetuximab was associated with a short median time to progression (TTP) of 2.1 months and a median overall survival (OS) of 10.4 months. Combination therapy was well tolerated (*Christina, et al 2013*). Carey et al. 2008 reported that adding cetuximab to carboplatin did not improve outcome. Few Studies evaluated the efficacy of small-molecule EGFR inhibitors, including erlotinib and gefitinib, as single agents in the setting of advanced breast cancer, with disappointing (*Dickler, et al 2009*, *Gutteridge, et al 2010*). TNBC presents a high rate of PTEN loss and AKT activation [33].EGFR inhibitor would not be effective in TNBC which showed PTEN loss. EGFR inhibitors should be developed as combination therapy with mTOR inhibitors. Interestingly, several papers also report that mTOR activation could lead to cisplatin resistance.

VEGF (vascular endothelial growth factor) inhibitors

TNBC is a highly proliferative neoplasm that needs constant angiogenesis throughout all the phases of its development, invasion and metastasis. The development of agents that inhibit tumor angiogenesis has been an active area of investigation in breast cancer. Bevacizumab, a humanized monoclonal antibody to VEGF. Strategies to inhibit tumor vessel growth include the use of bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor A (VEGF-A), and tyrosine kinase inhibitors (ie, sunitinib, sorafenib). Miller et al 2007 demonstrated a significant improvement in progression-free survivalwhen adding bevacizumab to paclitaxel chemo - therapy compared with single-agent paclitaxel alone in first-line treatment of metastatic disease. Women who received bevacizumab experienced a significantly higher objective response rate.

PARP (poly ADP-ribose polymerase) inhibitors

The PARP1 (poly ADP-ribose polymerase) gene encodes a chromatin-associated enzyme that modifies various nuclear proteins. The PARP enzyme fixes DNA damage in cells, including DNA damage caused by chemotherapy medicines. When PARP1 is inhibited, breaks in double-strand DNA accumulate that, under normal conditions, would be repaired via homologous recombination. Both BRCA1 and BRCA2 are required for the homologous recombination pathway to function. Scientists developed PARP inhibitors based on the idea that a medicine that interferes with or inhibits the PARP enzyme might make it harder for cancer cells to fix damaged DNA, which could make chemotherapy more effective. PARP inhibitors have recently shown very encouraging clinical activity in early trials of tumors arising in BRCA mutation carriers and in sporadic triple-negative cancers. One of these inhibitors, iniparib (also known as BSI-201), was recently used in a randomized phase 2 trial involving patients with triple-negative cancer When the inhibitor was added to a chemotherapy combination of gemcitabine and carboplatin, there were significant improvements in the rate of tumor regression. Similarly, the use of an oral PARP inhibitor, olaparib, often after chemotherapy had failed, resulted in tumor regression in up to 41% of patients carrying BRCA mutations, most of whom had triple-negative breast cancer (*Tutt, et al 2010).* Currently, many initial trials on targeted therapy with PARP inhibitors are underway to study their use in the treatment of TNBC. Several new agents are beinginvestigated that may be beneficial for patients with this subgroup of breast cancer.

mTOR (mammalian target of rapamycin) inhibitors

The mTOR (mammalian target of rapamycin) is associatedwith cell cycle regulation and an effector of the common pathway of phosphatidylinositol 3-phosphate phosphatase and PTEN/AKT pathway. mTOR is a potential targets in advanced TNBC. Inhibiting mTOR's mediated PI3K/Akt signaling pathway abolishes cellular proliferative responses and causes cell cycle arrest. As PI3K/Akt overactivity has been identified in a number of breast cancers rapamycin and its analogs temsirolimus, everolimus, and deforolimus, are undergoing clinical evaluation in TNBC treatment

Src tyrosine kinase inhibitors

Due to the significant role of Src in growth, proliferation, invasion, angiogenesis and metastasis has rationalized the need for the development of src inhibitors in breast cancer. Activation of src is associated with the activation of EGFR pathway which is frequently expressed in triple negative breast cancers (Thomas SM,et al 1997). Inhibition of src may reduce recurrence and metastasis in the residual disease and also slow down the disease progression. Dasatinib is an orally available tyrosine kinase inhibitor that targets Src. It is currently approved for the treatment of imatinib-resistant. Although dasatinib has been shown to inhibit the growth of basal/TN breast cancers in vitro, it is unclear whether this is mediated by inhibition of c-SRC or of related kinases that are also blocked by this compound Indeed, several reports have reported a lack of correlation between c-SRC/ phosphorylated-SRC levels and dasatinib growth inhibitory ability in preclinical studies. Dasatinib monotherapy in patients with breast cancer are disappointing

2. Conclusion

Current research strategies are aimed to understand the biology of TNBC with the goal of developing preventive measures and improving treatment strategies for this challenging disease. It is hoped that further advances in targeted treatment and optimization of chemotherapy will provide more effective treatment and improved outcomes for this subtype of breast cancer. The high frequency of disease recurrences with present standard therapies shows the importance of developing new therapeutics for breast cancer.

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