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RECENT ADVANCEMENTS IN THE MANAGEMENT OF TRIPLE NEGATIVE BREAST CANCER

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ABSTRACT

Breast cancer is the most prevalent cancer diagnosed among women around the world, occurring with a lifetime risk of one in eight. In US it accounts for one third of all cancers in women and out of which 15%–20% of breast cancers accounts for triple-negative breast cancers (TNBCs). TNBC is much higher in Asians i.e. 25-30%. Triple negative breast cancer does not express estrogen receptor, progesterone receptor and human epidermal growth factor. Usually this type of cancers shows aggressive behavior, distant metastasis and poor prognosis when compared to hormonal positive breast cancer patients. Patients with early stage tripe negative breast cancer patients have better chemotherapy response rates than other type patients but more likely to get early relapse, visceral metastasis, and shorter survival. Due to lack of expression of ER, PR and HER2, triple negative breast cancer patients will have less therapeutic options unlike hormonal receptor positive patients whom were greatly benefited from drugs like tamoxifen and transtuzumab which increases the survival of the patients. This subject review will focus on existing therapies and recent advancements in the treatment of triple negative breast cancer patients.

KEYWORDS: Triple Negative Breast Cancer, Luminal Cells, ER Negative And Positive.

INTRODUCTION

Morphologic features of tumor cells have long been validated for the clinical classification of breast cancers and are regularly used as a gold standard to establish prognostic outcomes in treating patients. Identification of conventional molecular markers such as expression of the receptors for estrogen (ER) and progesterone (PR) and the human epidermal growth factor receptor 2 (HER2) has played an important role in determining targets for the development of efficacious drugs for treatment and has also offered additional predictive value for the therapeutic assessment of patients with breast cancer. Recently technical improvements in identifying several cancer-related genes have provided further possibilities to identify specific subtypes of breast cancer. Triple-negative breast cancer (TNBC) has recently been recognized as an important subgroup of breast cancer with a distinct clinical outcome and therapeutic approach when compared to other subgroups of breast cancer. TNBC is primarily comprised of a molecularly distinct subtype of breast cancer, the basal-like subtype but not all the basal-like types are Triple-negative breast cancer. TNBC is defined by the absence of a target and there are limitations to employing a tailored therapeutic approach. Conventional cytotoxic therapies are the mainstay treatment in Triple-negative breast cancer. Active preclinical and clinical research programs focus on defining clinical behavior and exploring the risk factors for understanding the molecular biology of TNBC. It is mainly to improve prevention by selecting proper conventional agents and discovering novel therapeutic targets. Triple-negative breast cancer (ER, PR, and HER2-negative breast cancer) remains a major challenge to physicians.[1] Although TNBC accounts for a relatively small minority of breast cancer cases, it is responsible for a more number of breast cancer deaths. There are fewer advances in the treatment of TNBC than has been seen with other subtypes. so new research initiatives for TNBC are critical for patients as well as medical oncologists.

CLASSIFICATION

Usually, breast cancer was classified according to its morphologic features, histological type, and grade (severity). Identification of molecular markers such as expression of the estrogen and progesterone receptors and the human epidermal growth factor receptor 2 results in a better therapeutic assessment of women diagnosed with breast cancer. More recently, gene expression analysis using DNA microarray technology has identified additional breast tumor subtypes that were not apparent using traditional histopathology methods. Based on gene expression profiles, breast cancer can be divided into 5 main groups. It was based on

distinctive gene expression signatures.[2] There are two ER-positive subgroups and three ER-negative subgroups as follows.

ER POSITIVE SUBGROUPS (LUMINAL)

Most breast cancers originate from the inner luminal cells that line the mammary ducts. It was characterized by the expression of ER and luminal epithelial cell-related genes. Luminal A and luminal B tumors are similar in that both are typically ER+ or PR+ or both. However, they are dissimilar in that the A type is usually HER2– and the B type is more likely to be HER2+ and lymph node-positive. Women with luminal A types are diagnosed at a younger age. It's characterized by the best prognosis, with relatively high rates of overall survival and relatively low rates of recurrence. Those with luminal B tumors usually have a higher tumor grade and a poorer prognosis.

ER NEGATIVE SUBGROUPS

Basal-like, ErbB2þ, and normal-like showed an expression phenotype more similar to myoepithelial or basal epithelial cells. These intrinsic subtypes show different mutation patterns, prognoses, and routes of progression. Basal-like tumors originate in the outer basal cells that line the mammary ducts. Basal-like tumors are diagnosed more frequently among younger women and are associated with hereditary BRCA1-related breast cancers. They are often aggressive and are associated with bad prognosis than those for the luminal A and B and normal breast-like types. The HER2 tumors are named for their status as HER2+. They tend to be ER–, PR–, and lymph node-positive along with poorer grades. These tumors also contain p53 mutations. The HER2+ tumors have relatively poor prognoses and are prone to early and frequent relapse and distant metastasis. The ErbB2þ tumors were in particular characterized by high expression of ErbB2 and genes located adjacent to the ErbB2 locus and the normal-like subgroup showed expression patterns similar to normal breast tissue samples3. The normal breasts like tumors are those that do not fall into any of the other categories. They account for 6%–10% of all breast cancers. These tumors are usually small and typically have a good prognosis. They are more common in postmenopausal than in premenopausal women.[2]

TRIPLE NEGATIVE OR BASAL-LIKE BREAST CANCER

TNBCs are malignancies that are estrogen receptor (ER), progesterone receptor (PR), and HER2 negative. The subgroups of tumors have been focused importantly. It is due to, unlike tumors that are ER and/or HER2 positive, triple-negative tumors lack therapeutic targets. Due

to this conventional chemotherapy is the only effective systemic treatment for these patients and there is an urgent need for new treatment approaches. Secondly, recent developments in gene expression arrays have categorized breast cancer into distinct one of these subgroups as defined by genetic clustering of the basal-like group most of these are TNBCs. Because the gene array of tumor among the features of profiling is not clinically available, immunohistochemical surrogate profiles for the basal-like types was not standardized or validated. Clinicians do not have either direct or indirect access to the molecular subtype. so breast cancers in the clinical setting are more typically categorized by routine immunohistochemistry as TNBC. Even though most basal-like cancers are TNBC, there is a moderate disagreement between TNBC and Basal-like subtype. In addition to variability in the expression of known basal markers, there is also heterogeneity within TNBC for other potentially relevant features including p53 mutation, BRCA1 mutation or expression, and degree of expression of immune response genes.[3]

EPIDEMIOLOGY AND RISK FACTORS

Among the 1 million or more women worldwide who are diagnosed with breast cancer annually, an estimated 170,000 may be classified as having triple-negative breast cancer TNBC has not only a common pattern of molecular and histological characteristics but also distinct patterns of epidemiology and risk factors, especially when compared with hormone receptor (HR) positive luminal breast tumors. Risk factors for TNBC have differed based on populations but compared with luminal tumors, triple-negative basal tumors are more likely to arise among women with younger age, younger age at full-term pregnancy, shorter duration of breastfeeding, use of drugs that suppresses lactation, higher body mass index, and waist-to-hip ratio, and metabolic syndrome.[4] Evidence suggests that menopausal status and race are also crucial risk factors. An increased risk of TNBC has been shown in premenopausal women and African American women. Among breast cancer patients in the United States, African-American women have a substantially higher mortality rate than Caucasian women. In the United Kingdom, women of African descent present with breast cancer at a younger age on average and have twofold higher mortality than Caucasian women Data from the California Cancer Registry showed that African American women with late-stage TNBC had the poorest survival of any breast cancer subgroup. There is also some evidence for a slightly Better prognosis with TNBC among Asian women than among Caucasian women. Additionally, the prevalence of TNBC among Hispanic women with breast cancer was relatively high.

PHARMACOTHERAPY OF TNBC

Currently accepted specific molecular targeted agent doesn't exist for triple-negative breast cancer however, it responds well to chemotherapy. TNBC patients who have seem to benefit the most from cytotoxic agents in the adjuvant setting. As neoadjuvant chemotherapy patients with TNBC and HER2 amplification have better response rates, as well as a more frequent incidence of a pathological complete response (pCR) when receiving 5-fluorouracil (5-FU), doxorubicin and cyclophosphamide. There is no preferred agent in the neoadjuvant setting, although more data definitely may be needed related to whether anthracycline/taxane-based therapies should remain the standard approach.

PLATINUM AGENTS

A group of agents which was gaining importance in the management of patients with TNBC was the platinum compounds, partially based on their ability to bind directly to DNA. This causes the DNA to crosslink, resulting in double-strand DNA breakage. In preclinical models, those neoplastic cells with BRCA mutations are consequently more susceptible to agents that induce DNA damage. Women with BRCA mutations who received neoadjuvant treatment with cisplatin had improved responses compared to other agents. The features of some BRCA mutation-related breast cancers and TNBC are similar and has been hypothesized that TNBCs are also specifically sensitive to platinum agents. This remains controversial as to date there was no randomized trials that demonstrated the benefit of platinum versus other agents.[5] Cisplatin was given in a combination with other cytotoxic agents for neoadjuvant treatment. It has also been used with epirubicin and 5-FU a pCR of 40% was achieved. A study of 74 patients treated with cisplatin, epirubicin, and paclitaxel along with G-CSF shows a higher rate of pathological complete response. These results encouraging but further validation and testing were required. CCALGB40603 and NCT00432172 trials are exploring carboplatin as an agent in TNBC along with cyclophosphamide and epirubicin. Phase II Translational Breast Cancer Research Consortium 009 trial is evaluating the response rate of metastatic breast cancer patients treated with cisplatin or carboplatin. The expression of p63/p73 as a potential biomarker of platinum sensitivity is of concern as these proteins are expressed in one-third of patients with TNBC .In another study phase III trial currently underway in the UK, women with TNBC randomized to carboplatin or docetaxel with crossover at progression.[6]

ANTI-TUBULIN AGENTS

A recent anti-tubulin agent available for the treatment of breast cancer is ixabepilone. This drug was similar to taxanes and ixabepilone stabilizes microtubules and causes cell cycle arrest and apoptosis. It has the advantage of bypassing the resistance mechanisms associated with drug efflux pumps and specific paclitaxel resistance associated with b-tubulin. Two phases III clinical trials were currently undergone on ixabepilone with capecitabine versus capecitabine alone. A subset analysis of women with TNBC identified an improved overall response for this combination of 31% versus 15% and progression-free survival (PFS) of 4.2 months versus 1.7 months. When used as neoadjuvant treatment with ixabepilone led to a pCR in 26% of the 42 women with TNBC6. A retrospective study revealed that resistance to taxanes was correlated with the expression of beta-III tubulin, Patients with a basal-like phenotype had a higher expression of beta III-tubulin, and its expression was predictive of response to therapy. Further studies of the potential role of this as a predictive marker are needed before conclusions can be reached.

MITOTIC INHIBITOR

Another novel mitotic inhibitor currently being studied for the treatment of breast cancer is Eribulin. A recent phase III trial compared Eribulin against several investigator-chosen regimens for the treatment of women with refractory metastatic breast cancer. Improved survival in favor of those women taking Eribulin was observed. Of the patients enrolled in this trial, 20% had TNBC. The subset analysis for this trial has not been yet reported.

TARGETED THERAPIES

Poly (ADP) ribose polymerase 1 (PARP1) is a nuclear protein that is recruited to the site of damage after the induction of both single and double-stranded DNA breaks. PARP1 catalyzes the transfer of ADP-ribose polymers from NAD+ to target proteins and modulates DNA restoration by activating and recruiting important components of base excision repair pathways such as XRCC1. PARP1 also contributes to the modification of histones, which leads to local chromatin remodeling allowing access of DNA repair proteins to the repair site. The inhibition of PARP1 accelerates the effects of ionizing radiation, DNA methylating agents, topoisomerase I inhibitors, and platinum compounds.[7] When PARP1 is inhibited in normal cells, DNA repair happens through the homologous recombination pathway in which BRCA plays a key factor. Cells which are deficient in BRCA are more dependent on PARP1 to maintain genomic integrity. Its inhibition thus leads to synthetic lethality, a process that

occurs when the inactivation of either of the two genes individually has no effect but combining the mutations is lethal. Several PARP1 inhibitors are at different stages of clinical development, olaparib (previously known as AZD2281) has been evaluated in a phase 1 study where 60 patients with breast cancer were enrolled. Results show that nine patients had an objective response. Mainly the responders had abnormalities in one of the BRCA genes. Olaparib was further evaluated in a phase II study that enrolled 54 patients with known BRCA-mutated breast cancer. 27 patients received 400 mg twice per day, of which 11 (41%) experienced a response with a median PFS of 5.7 months. A second cohort of 27 women received 100 mg of olaparib twice per day. Results have shown that 6 patients (22%) experienced a response with a median PFS of 3.8 months. This agent was well tolerated and nausea and fatigue are the most common adverse events. Several clinical trials using olaparib in women with BRCA-deficient cancers are in different stages of development. In a phase 2 study, 120 patients were randomized to gemcitabine and carboplatin alone or the same combination plus the intravenous PARP1 inhibitor, iniparib. The addition of iniparib led to an improved response rate, as well as PFS. The addition of iniparib was tolerated well with fewer adverse effects compared to the standard arm. Iniparib is also being evaluated in 2 neoadjuvant clinical trials, a single-arm trial studying the combination of iniparib, carboplatin, and gemcitabine. The other one is a Spanish study in which received either iniparib plus paclitaxel versus paclitaxel alone. The preliminary results are encouraging. Veliparib (ABT-888) is another PARP 1 inhibitor being evaluated in breast cancer. In a recent trial report on temozolomide where 41 women with metastatic disease were recruited, of which 23 (56%) of patients have TNBC women who were deficient for BRCA1 had Median PFS higher than others.[7]

EGFR

Some studies suggest that TNBC expresses EGFR in nearly half of the cases. Its expression is found to be associated with an inferior outcome. A phase II study of cetuximab an EGFR monoclonal antibody followed by carboplatin on progression was compared with concomitant cetuximab and carboplatin. When used in combination with carboplatin, it led to overall clinical benefit in 19 of the 71 patients enrolled. In a separate randomized phase II study, the addition of cetuximab to Irinotecan and carboplatin increased response. A fully humanized antibody against EGFR, panitumumab, is currently evaluated in combination with gemcitabine and carboplatin in TNBC.EGFR receptor inhibition can also be mediated with the use of small molecules that inhibit the tyrosine kinase domain of this receptor8. Erlotinib

is currently being evaluated in combination with docetaxel and carboplatin in patients with metastatic TNBC.

ANTI-ANGIOGENIC AGENTS

Angiogenesis as a process was required for tumor growth, invasion, and metastasis in several malignancies, including breast cancer. This process can be targeted for therapeutic purposes through several mechanisms. The vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis. VEGF expression was expressed well in patients with TNBC, compared to other subtypes. Bevacizumab, a humanized monoclonal antibody against VEGFA, was proven to be effective in metastatic breast cancer in several phase III clinical trials.[8] In E2100 study that evaluated this agent along with paclitaxel had an improved overall response rate of 48% versus 33% in those who received paclitaxel alone. AVADO trial evaluated docetaxel alone or with two different doses of Bevacizumab (7.5 and 15 mg/kg every 3 weeks). When compared to the placebo, PFS was superior in both Bevacizumab arms and the 15 mg/ kg arm was found to be better. The RIBBON-1 trial proved that Bevacizumab increased PFS and overall response rate when compared to placebo when this agent was used with single-agent taxanes, anthracycline-based regimes, and capecitabine. Patients with TNBC demonstrated an improvement in PFS when Bevacizumab was used both with capecitabine. Progression-free survival was also improved when given a combination of taxane/anthracycline. Bevacizumab is currently evaluated in TNBC by several independent studies. A phase II neoadjuvant study of patients receiving paclitaxel with or without carboplatin and this combination with or without Bevacizumab was going on. The second study, BEATRICE was a phase III adjuvant study where several chemotherapy regimens and different doses of Bevacizumab are being evaluated in patients with TNBC. This trial was recently completed and the results are eagerly awaited.

SRC TYROSINE KINASE INHIBITOR

SRC tyrosine kinase is a non-receptor signaling kinase that functions downstream of several growth factor receptors i.e. PDGFR, EGFR, IGF-1R, and HGFR. It plays an important role in cancer cell proliferation and invasion through multiple pathways. SRC is deregulated in breast cancer so it emerged as a potential therapeutic target. Gene expression profiling of breast cancer cell lines reveals two groups independently identified a gene expression pattern that was predictive of sensitivity to dasatinib, a multitargeted tyrosine kinase that targets important oncogenic pathways, including the SRC family kinase. This gene signature was

present more commonly in both cell lines and in patients who had a triple negative profile. However, dasatinib studied as a single agent in TNBC yields poor results. Currently, trials using gene expression patterns as a tool can predict response to dasatinib as a single agent in different subsets of breast cancers are going on.[9]

MULTIKINASE INHIBITORS

Multi kinase inhibitor with antiangiogenic properties, sunitinib, was evaluated as a single agent in a phase II study, where it was found to induce a response in 11% of a pretreated cohort of metastatic breast cancer patients in addition to carboplatin and paclitaxel as adjuvant treatment for TNBC. The mammalian target of rapamycin (mTOR) is a protein that is downstream of the PI3K/AKT pathway and, when activated, promotes protein synthesis and angiogenesis. Everolimus, an mTOR inhibitor, has shown a response when used as a single agent in heavily pretreated patients with metastatic breast cancer. It is evaluated as a single agent in phase II clinical trials in patients with metastatic TNBC and another placebo-controlled neoadjuvant randomized phase II study along with cisplatin and paclitaxel in patients with stages II and III TNBC.[10]

ANTI-ANDROGEN AGENTS

Genome-wide gene expression profiling study of 99 patients with breast cancer of which 41 of whom had triple-negative disease revealed TNBC clustered together with the ER-positive group. When focusing on only those patients with TNBC, the nine ERdiscordant samples closely correlated with each other and were contained in a single cluster. Further characterization of this subtype of TNBC showed that it had a molecular resemblance to ER-positive tumors and expressed genes that are targets of the ER. Most of the patients in this group expressed the androgen receptor.[11] Several studies have established 10-35% of TNBC express the androgen receptor. Preclinical data have given support to the development of a phase II trial using bicalutamide, an antiandrogen, in the treatment of TNBC that is androgen receptor positive.

RECENT DEVELOPMENTS

New studies using high throughput technologies to assess gene expression and genomic copy number variations have provided insight into the heterogeneity of TNBC and also identified potential new targets. Among the targets is the fibroblast growth receptor (FGFR), which is part of an important signaling pathway found to be deregulated in several malignancies.[11] FGFR1 is over-expressed in up to 5.5% of patients with TNBC. Several tyrosine kinase

inhibitors that target the FGFR receptor are currently in different stages of drug development. TKI258 which is an FGFR inhibitor is currently being evaluated in a phase II study of women with HER2-negative breast cancer. Another attractive target is the RAS-mitogen-activated protein kinase (MAPK) signaling pathway, as it plays a central role in regulating the growth and survival of neoplastic cells. Several inhibitors of the mitogen-activated protein kinase (MEK) an essential component of this pathway are in clinical trials for various malignancies including breast cancer. Preclinical studies have demonstrated that the inhibition of MEK leads to the activation of the phosphatidylinositol 3-kinase (PI3K) pathway which was found to be deregulated in 30% of patients with basal-like breast cancer this feedback counteracts the effects of MEK inhibition on cell cycle and apoptosis induction. The dual blockade, with inhibitors of both PI3K and MEK, synergistically inhibits the growth of basal-like breast cancer cells in vitro and in vivo this combination needs to be evaluated in women with TNBC. By using transcriptional profiling data the expression of the human kinome was evaluated. They were able to identify a set of kinases differentially expressed and critical for the growth of ER-negative breast cancer. In this study, two groups of TNBC were identified, a subset defined by kinases involved in cell cycle checkpoint control and mitogenesis i.e.CHK1, BUB1, TTK, and AK2.Another subset was defined by kinases involved in the S6 kinase-signaling pathway, which includes the RPS6KA3, SMG-1, and RPS6KA1 kinases. SiRNA knockdown experiments to down-regulate the expression of several of the kinases of interest and established that of the 20 kinases evaluated, 14 were critical for the growth of ER-negative breast cancer cell lines. The majority of these kinases were an attractive therapeutic target.[12] In addition, ongoing research is exploring the possibility of inhibiting the proliferation of TNBC tumors by targeting other cellular pathways. C-KIT and platelet-derived growth factor receptor β and trabectedin (Yondelis) which binds to the minor groove of DNA to disrupt cellular function and induce apoptosis, are undergoing evaluation in phase II trials that are prospectively designed to evaluate efficacy in TNBC.[12] Therapeutic strategies that target the epigenetic modifications that may be present in breast cancers may also prove efficacious in TNBC, although the current clinical trials are not limited. Some promising agents include inhibitors of histones deacetylases (HDAC) such as vorinostat (Zolinza), trichostatin A, and investigational butyrate derivatives. The results of at least some of these studies are likely to have an impact on the way TNBC is treated in the future.

CONCLUSION

TNBC is a heterogeneous disease characterized by a lack of ER, PR, and HER2 expression. The design of clinical trials should be based on strong biological rationale and emphasis must be given to biologically preselected populations followed by the identification of predictors of response and validation before entering into phase III trials. It ensures successful drug development and reduced cost. In the absence of standards for staining and scoring of basal markers using conventional methods focus should be given to developing new methods which will allow for rapid conversion of results into clinical application. Molecular biology-driven research can identify novel targets and greater sensitivity for distinguishing various subtypes of triple-negative breast cancer. On-going research on triple-negative breast cancer will have an impact on the pharmacotherapy of triple-negative breast cancer and personalized therapy for TNBC is eminent soon

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