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Advances of Non-Surgical Therapy for Different Molecular Subtypes of Breast Cancer

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Introduction

Breast cancer is one of the most commonly diagnosed and leading cause of death in women. It has been estimated that 25% of the cancer cases are due to breast cancer alone and accounts for 15% cancer related deaths in women [1]. Breast cancer is a complex and heterogeneous disease categorised into different molecular subtypes having different various prognoses. The understanding of the specific biology of the different subtypes is important for the treatment plan [2-6].

Gene expression profiling has helped to identify the major breast cancer subtypes beyond the hormone receptor positive and hormone receptor negative types. The luminal A and luminal B are the hormone receptor positive cancers while the HER2 and basal-like are the major subtypes identified as the hormone negative cancers. Approximately 70% of invasive breast cancers are Estrogen Receptor/Progesterone Receptor (ER/PR) positive, 15% are ER/PR negative, Human Epidermal Growth Factor Receptor 2 (HER2) positive and also 15% of the invasive ductal carcinoma are basal-like i.e., ER/PR/ HER2 negative. In case of the ER/PR positive type i.e., luminal type, some overexpress HER2 [7-13].

Breast Cancer Subtypes

Luminal breast cancers or the hormone receptor positive breast cancers accounts for the largest portion of the breast cancers diagnosed i.e., about 70%. Breast cancers expressing high levels of ER but low expression of HER2 with low histological grade and low proliferation rate are categorised as luminal A intrinsic subtype [3,14]. While Luminal B is of higher histological grade and are more aggressive than that of Luminal A [15]. The TP53 pathway is conserved in the luminal A but frequently inactivated in the luminal B. Luminal A breast cancers are less responsive to chemotherapy and is dependent on the antiendocrine therapy while luminal B shows response to chemotherapy and do not respond to antienstrogen therapy [14]. Of all the subtypes of breast cancer Luminal A has the best prognosis [6].

HER2 positive breast cancers are characterised by the over-expression of HER2 protein [16]. Apart from the rest of the members of the HER family, over-expression of the HER2 is considered as an important feature that leads to the induction of carcinogenesis. This subtype expresses high level of proliferative genes and genomic instability [14]. They are chemosensitive but categorised as a poor prognosis subtype until the introduction of the HER2 targeted drugs [14]. Expression of HER2 is the prognostic and predictive marker for the HER2 targeted therapy [16].

Basal-type is also commonly known as the triple negative breast cancer as this subtype of breast cancer is negative for ER/PR/HER2 [17]. They are defined as triple negative breast cancers (TNBCs) [14]. It occurs most commonly in the younger group of women, in Afro-Americans and in the group of women having BRCA gene mutated [17,18]. This subtype is associated with increased genomic complexity and less stable in comparison to the other subtypes [14]. They are chemoresponsive but have shown to be a poor prognosis subtype [14]. Despite the extensive researches taking place, this subtype lacks specific targets for therapy [19].

Early detection of breast cancer by mammogram enables the removal of the tumor at an early stage by surgery [6]. But, it has been reported that in a study of a 30 year follow-up of breast cancer patients about 90% of the women treated with surgery alone, the mortality rates exceeds 50%. This indicates the microscopic dissemination of the disease from the local area which may recur back even after complete surgical resection. Hence, to eliminate or suppress the disease led to the advent of systemic adjuvant therapy, including chemotherapy, endocrine therapy and targeted therapy. It had improved the outcomes of the patients with early breast cancer [20-22]. Adjuvant therapy has been considered as the gold standard for breast cancer treatment. But recently, neoadjuvant therapy has been stated as a standard treatment option [6,23]. Here, we will review the different treatment type with relation to the stage of the cancer and the molecular subtypes.

Adjuvant Therapy in Luminal Cancers

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published report on randomized controlled trials (RCTS) in 2005 of adjuvant chemotherapy or hormonal therapy that began in 1995 [24]. The result reported a reduction of about 50% of the overall mortality in 15 yrs, when the breast cancer patients who were hormone receptor positive received adjuvant chemotherapy and tamoxifen for 5 yrs after the surgery [24]. The anthracycline based regimen achieved the recurrence free survival by about 8% when compared with the untreated group. Cyclophosphamide, methotrexate and fluorouracil (CMF) was first introduced by Bonadonna et al., and is one of the oldest poly-chemotherapy regimen developed for the breast cancer treatment [25]. The CMF improved the survival and gained recurrence free survival by about 10% [26]. There was a comparison between the CMF with the anthracycline based regimen such as FAC (5-fluorouracil-doxorubicin-cyclophosphamide) or FEC (5-fluorouracil-epirubicin-cyclophosphamide). The study not only reported the long term benefits of the 6 months polychemotherapy with FAC or FEC but also reported a reduction in the annual breast cancer death rate by 38% for women less than the age of 50 and by 20% for the women between the age of 50-69. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-11, B-12 trials showed that the Stage II breast cancer patients who had received doxorubicin plus melphalan and fluorouracil (PF) improved the DFS (Disease Free Survival) and OS (Overall Survival) in 6 yrs compared to those patients who received the

same regimen excluding doxorubicin [27]. In another trial, where NSABP B-16 compared 4 cycles of AC (Adriamycin and Cyclophosphamide) regimen plus tamoxifen and tamoxifen alone as an adjuvant therapy, there was a reduction of about 15% in the relapse or death with 25% risk reduction in comparison to tamoxifen only at 10 yrs follow-up. The anthracycline based regimen presented an overall reduction in the breast cancer related morbity and mortality than that of CMF [28]. This has led to the initiation for the development of anthracycline based poly-chemotherapy as an adjuvant therapy.

The introduction of taxane with better efficacy in advanced breast cancer led to the incorporation of docetaxel in the adjuvant settings in the Breast International Trial (BIG) 02-98 trial. The trial led to the finding that the docetaxel arms presented improved survivals for the lymph node positive breast cancer [29]. In another trial involving the TAC (docetaxel, doxorubicin, and cyclophosphamide), or FAC (fluorouracil, doxorubicin, and cyclophosphamide), with the DFS as an end point study revealed that the TAC group has a better DFS and OS compared to OS group at a 10 yr follow-up [30]. From the various trial studies and from the EBCTCG meta-analysis, was observed there was a reduction in the recurrence and mortality by adding taxane to the anthracycline regimen [26].

Another study, was undertaken to reduce the burden of chemotherapy in adjuvant therapy, by the Shulman et al., involving the use of single agent Paclitaxel, doxorubicin and cyclophosphamide. This study showed that the use of the single agent paclitaxel induces less toxicity in comparison to that odf doxorubicin and cyclophospahmide [31].

Adjuvant endocrine therapy is categorised in two main agents: selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). The SERMs competitively bind to ERs and comprises of three main drugs: tamoxifen, raloxifen, and toremifene. While the AIs works by the process of aromatization and inhibits the enzyme 'aromatase'. Exemestane, anastrazole and letrozole comprises the AIs [32]. Tamoxifen was developed during 1960s and responded to the metastatic condition of breast cancer [33]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) stated that there was a reduction of about 31% mortality in tamoxifen-treated patients [34]. Treatment with tamoxifen resulted in an extended DFS [35,36]. The EBCTCG also concluded that tamoxifen treatment in the hormone positive breast cancer patients reduced the recurrence rate by about 13% and mortality rate by about 9.1% [34].

The adjuvant therapy in ER positive post-menopausal patients, the choice of regimen is AIs as it provides better outcomes compared to tamoxifen [37-41]. In a trial to compare the efficacy of anastrazole and tamoxifen for postmenopausal women, ATAC was given (anastrazole, tamoxifen, alone or in combination). A prolonged DFS and reduced metastatsis was resulted sinificantly in the anastrazole group in comparison to the tamoxifen group after a median follow-up of 68 months [42]. In another case, in phase three trials, Tamoxifen and Exemestane Trial (TEXT) and Suppression of Ovarian Function Trial (SOFT), in which the premenopausal women with ER positive breast cancers were given exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for a period of 5 yrs. There was an increase in the DFS by 3.8% in the exemestane plus ovarian suppression group when compared to tamoxifen plus ovarian suppression group after a median follow-up of 68 months [43]. In the MA-17 trial of National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), a group of post-menopausal patients, who had previously given tamoxifen for 5 years, were assigned to receive 5 years of letrozole or a placebo. After the follow-up of 4 years, the DFS was about 94.4% in the letrozole group and a reduction in the disease recurrence in comparison to the placebo group [44]. In another trial, BIG-98 trial that suggests the superiority of letrozole from tamoxifen in the endrocrine therapy consisted of three groups in which one group received letrozole for 5 years, another one received tamoxifen for 5 years and the last one received sequential therapy. The letrozole group presented a superior outcome while the outcome of tamoxifen followed by letrozole was the same as using letrozole alone [45].

Adjuvant Therapy in HER2 Positive Breast Cancers

Trastuzumab is the first monoclonal antibody developed as an anti cancer therapeutic. It binds to the juxtamembrane domain of HER2 receptor [46] and downregulates the HER2 dimerization and signalling cascades downstream of HER2 including the PI3K/AKT/mTOR pathway [14]. It has been reported that in large phase III trials, addition of trastuzumab to postoperative chemotherapy for 1 year reduced the risk of recurrence by one-half approximately and risk of death from breast cancer by one-third [14]. In the Breast Cancer International Research Group (BCIRG) trial, a comparison between three groups were made: AC-T (adriamycin, cyclophosphamide, and paclitaxel), AC-TH (adriamycin, cyclophosphamide, paclitaxel and trastuzumab), and TCH (docetaxel, cyclophosphamide, and trastuzumab). The AC-T group resulted in 75% DFS, AC-TH with 84% and TCH with 81% DFS after a median follow up of 65 months. In another study conducted by Tolaney and Barry, consisting of 406 patients with node negative tumors less than 3 cm were given paclitaxel plus trastuzumab for 12 weeks, followed by 9 months of trastuzumab. Interestingly, only four recurrences were observed which suggested an good approach for the selected patients [47]. In addition, a subcutaneous trastuzumab presented a safety and an efficient approach in comparison to standard intravenous administration [48]. Besides being a valid treatment option, subcutaneous trastuzumab was preferred by most of the patients [49]. Resistance to trastuzumab therapy still being a challenge to the treatment of HER2 overexpressing breast cancer, lapatinib, a small molecule, was developed to overcome the resistance. It inhibits HER2 as well as HER1. But lapatinib faced failure when a set of the patients were grouped into lapatinib and placebo without trastuzumab resulted in 13% DFS in lapatinib to 17% in placebo group at 47.4 months follow-up study [50]. Newer agents have been developed which are targeting HER2 overexpression in breast cancer: TD-M (emtansine-trastuzumab conjugate), and pertuzumab. These agents have been approved by the US FDA [51].

Adjuvant Therapy in Triple Negative Breast Cancer

This subtype of breast cancers responds very well to both anthracycline or taxane based regimen. The regimen for therapy is the same as that of the hormone positive cancers [52,53]. Triple negative breast cancers (TNBCs) have a mutation in the TP53 and respond to platinum treatments as has been reported that breast cancer cells exhiviting mutation in the p53 family proteins are sensitive to platinum agents [54]. Platinum agents like carboplatin is also used for the treatment of the TNBC as this subtype has a reduced capacity to repair DNA damage [55,56]. 'Dose dense' therapy is another approach for the treatment of the TNBCs. Based on the analysis of Cancer and Leukemia Group B (CALGB 97-41) trial at 6 years of median follow up, this therapy may serve as a valid option [57,58]. From different CALGB trials where two different chemotherapy regimens, CAF (cyclophosphamide, adriamycin, 5-FU) with dose dense Q2 weekly

AC-T were compared, a relative reduction of 55% and an absolute reduction of 28% were obtained for the TNBCs [58]. Treatment including the anti angiogenic strategies are taken up as the metastasis depend on angiogenesis [59,60]. This suggests the efficacy of VEGF targeted therapy [61].

Neoadjuvant Therapy in Luminal Cancers

Despite the limitations in neoadjuvant therapy like slow rate of response of tumors, longer duration of therapy etc in the hormone receptor positive breast cancer patients, trials had been carried out on the use of neoadjuvant therapy [62,63]. A trial was conducted on the use of endocrine therapy as a neoadjuvant therapy in a group of postmenopausal women, who were not fit for chemotherapy, aiming to change from mastectomy to breast conserving operation. A significant high response was obtained from the AI group in comparison to the tamoxifen group [64]. In another trial, the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial where response rate in postmenopausal women were compared between anastrozole, tamoxifen and combination group. A similar response was obtained whilst degree of surgery was reduced to breast conserving surgery from mastectomy [65]. In case of neoadjuvant chemotherapy in hormone receptor positive breast cancer, personalised neoadjuvant cytotoxic therapy is preferred over the standardised one [6]. Some of the well-known chemotherapy regimens used are Anthracycline/taxane based chemotherapy, AC, docetaxel, pacitaxel, epirubicin etc. [6,66,67].

Neoadjuvant Therapy in HER2 Positive Breast Cancers

It has been reported that the addition of trastuzumab in the preoperative chemotherapy increased the rate of pathologic complete response (pCR) from 22% to 44% and from 16% to 32% in the NeOAdjuvant Heceptin study and phase III GeparQuattro study respectively [14]. This leads to the recognition of chemotherapy plus tratuzumab as a standard care in the neoadjuvant therapy. Another small molecule inhibitor of both the EGFR (HER1) and HER2 kinases known as Lapatinib exert antitumor effect by inducing apoptosis and growth arrest along with blocking the downstream MAPK and AKT signalling pathways. It has been reported from a phase II study that a combination of lapatinib and trastuzumab a better therapy than that of trastuzumab or lapatinib alone in combination with paclitaxel followed by FEC in HER 2 positive breast cancers [68]. The trial conducted by the Taxol Epirubicin Cyclophosphamide Herceptin NeOadjuvant (TECHNO) utilizing EC (epirubicin+cyclophosphamide) and TH (paclitaxel+trastuzumab) appear as promising [69]. In another trial (NSABP B-41), it has been studied the comparison between lapatinib with ACT and lapatinib and trastuzumab and ACT [70]. After the Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation (NeoSphere) trial on the use of ertuzumab, trastuzumab and docetaxel, the US FDA accepted the use of pertuzumab in combination with trastuzumab and docetaxel as a neoadjuvant therapy of HER2 positive breast cancers [6].

Neoadjuvant Therapy in Triple Negative Breast Cancer

It has been reported from the NSABP-18 trial that the comparison between the groups with neoadjuvant therapy and non-neoadjuvant therapy, resulted in a more success in the breast conserving surgery in neoadjuvant therapy. In the case of chemotherapy given to the TNBC patients, the clinical outcome of the patients receiving platinum-based therapy was better than that of the patients who did not received the platinum-based therapy [71]. In a study consisting of 12 women with BRCA1 associated TNBCs receiving cisplatin for 4 cycles, 83% of women achieved pCR in contrast to 10-22% of women achieving pCR with anthracycline or taxane based therapy. In a phase II study of single-agent platinum in TNBC by the Translational Breast Cancer Research Consortium, observed approximately 30% in the response rate (RR) and 34% in the clinical benefit rate [14].

Conclusion

The advent of the adjuvant as well as the neoadjuvant therapy in the breast cancer patients has tremendously increased the outcome of the patients in the last few years. But the greatest challenge to the clinicians in the breast cancer treatment like the metastasis of the primary tumor or recurrence of the disease is still a nightmare. A thorough study of the fundamentals of the complex heterogenous disease will enable a better advancement of the therapeutic approach. A better understanding of the disease might improve the design of the clinical trials for a better therapeutic approach.

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