Targeted Therapies in Breast Cancer Management

Bharat Bhosale

According to GLOBOCAN 2018, breast cancer is the most frequently diagnosed cancer and is a common cause of cancer-related death in women in India.[1] Pathologically breast cancer is a heterogeneous disease and it is challenging to diagnose and treat. Global incidence patterns are influenced by risk factors and the availability of mammography. North America, Australia, New Zealand, and Northern and Western Europe have the highest breast cancer incidence rates. Mortality rates are influenced by the occurrence of the disease and the availability of screening programmes and appropriate treatment. Despite lower breast cancer incidence, breast cancer mortality rates are higher in many low income countries because of later stage at diagnosis, suboptimal access to treatment, more aggressive biological subtypes, and younger age at diagnosis.[2,3]

Breast cancer can be classified by molecular and histopathological features. The most common histologic subtype of all invasive breast cancers is infiltrating ductal carcinoma (80% to 85%). infiltrating lobular carcinoma accounts for approximately 10% to 15% of cases, whereas other rarer histologic subtypes account for 1% or less. Approximately 75% of patients with breast cancer have hormone receptor (HR)-positive disease. that is, oestrogen receptor (OR) and/or progesterone receptor (PR) expression of 1% or more. Furthermore, 15% to 20% of breast cancers are human epidermal growth factor receptor 2 (HER2)-positive as determined by HER2 protein overexpression measured by immunohistochemistry or gene amplification measured by fluorescence in situ hybridisation.[2-6]

The data on receptor status of breast cancers in India is limited. According to a couple of studies carried out in Tata Memorial Hospital, Mumbai approximately 50 to 60% of patients with breast cancer have oestrogen receptor (OR)-positive disease. Also about 30% patients have both OR and PR +ve disease. A retrospective study conducted by Nair et al in 2009 suggests that the percentage of HR +ve patients in early breast cancer and locally advanced breast cancer were 58.7 and 51 respectively. The domestic data on Her-2_{neu} receptor status is not available.[7-9]

With respect to prognosis of any breast cancer, one depends on the receptor status, grade and stage of the disease. A patient will have poor prognosis if the tumour is a stage IV disease or; a high grade tumour or; if the receptor status is HER2+ or triple negative. The median overall survival of metastatic breast cancer (MBC) is about 2 to 3 years.[2] Although it is still an incurable disease for more than 90% of MBC patients, much progress has been made in the past decade. The inadvertent use of existing drugs has

Consultant Medical Oncologist, BHIMS, 12, New Marine Lines, Mumbai-400020.

caused an emergence of resistance of tumour cells to a few existing molecules. Thus there is an urgent need for newer targets and drugs to find alternate means to prolong the survival of patients suffering from MBC with poor prognosis.[2,3-8]

Advanced breast cancer is an area where the existing drugs are not improving longevity or quality of life of patients. Thus, extensive drug research has focussed on this niche area in the past few years and newer targets have come into light. Discussed here are some of the newer therapies that have shown promise for treatment of advanced and metastatic breast cancer.

1. CDK4/6 inhibitors

CDK4 and CDK6 are mediate cell growth proliferation through the signaling cascade and act during the G1 phase of cell cycle. Drugs such as palbociclib, ribociclib, and abemaciclib are inhibitors of CDK. The combination of these drugs with endocrine therapy has synergistic effects in ER+ human breast cancer cell lines as well as in tamoxifen-resistant breast tumour. Besides their anti-proliferative activity, CDK inhibitors have shown strong anti-metastatic activity in a dose-dependent manner through reducing cyclo-oxygenase-II expression which is a gene promoting growth of tumour. Out of the three only palbociclib and ribociclib are available in India. Palbociclib is approved as first line treatment option in postmenopausal metastatic breast cancer patients along with Letrozole and in second line along with fulvetsrant. Ribocilib is approved in pre and post-menopausal females with metastatic breast cancer.[2-6]

1. PD1 and PD-L1 antibodies

Cytotoxic T-lymphocyte antigen 4 (CT LA-4). programmed death-1(PD-1), and programmed death-ligand 1 (PD-L1) all increase the immune response against the tumour by blocking immune-regulating proteins that downregulate the immune system. Antibodies to CTLA-4. PD-1 and PD-L1 have increased response rates in melanoma, non-small cell lung cancer, renal cell carcinoma. Hodgkin lymphoma. urothelial carcinoma. And squamous cell carcinoma of the head and neck. This class of drugs are also called checkpoint inhibitors. Atezolizumab and Nab-Paclitaxel in advanced triple-negative breast cancer have shown progression free survival advantage.[2-6,10]

1. Tyrosine Kinase inhibitors

Tyrosine kinase inhibitors are targeted therapies for cancer. Tyrosine-kinase inhibitors include neratinib. which is FDA-approved for the treatment of HER2-positive early breast cancer, and lapatinib, which is FDA-approved for the treatment of HER2-positive metastatic breast cancer. Other tyrosine kinase inhibitors, including neratinib and tucatinib, are under study for use in metastatic breast cancer treatment.[2-6]

1. PARP inhibitors

Poly (ADP-ribose) polymerase (PARP) are nuclear enzymes which facilitate DNA replication & repair. In a tumour cell the activity of PARP is significantly increased due to high cell turnover rate. In cells with wild-type BRCA1/2. Double-strand breaks are repaired via homologous recombination. but in BRCA1/2-deficient

cells with homologous recombination deficiency (HRD), DNA strand breaks rely on PARP-1 functionality for repair. PARP inhibition results in double-strand breaks in replicating cells. Up to date, three typical PARP inhibitors-olaparib, rucaparib, and niraparib, have all received their FDA approval for advanced ovarian cancer and/or primary peritoneal cancer with or without germline and/or somatic mutations in BRCA1/2. In the setting of breast cancer, a proof of concept study was conducted to assess the efficacy, safety, and tolerability of olaparib alone in women with BRCA1 or BRCA2 mutation advanced breast cancer. Patients had been given a median of three previous chemotherapy regimens.[2-6]

1. Antibody-drug conjugate

Approximately 18-20% of invasive breast cancers are HER2-positive subtype with poor prognosis in the absence of anti-HER2 treatment.[11,12] Trastuzumab emtansine (FDM1) is a complex compound produced by the conjugation of trastuzumab and the potent cytotoxic drug maytansine derivate (DM1). It is the first antibody-drug conjugate (ADC) developed specifically for the treatment of HER2- positive breast cancer. The binding of T-DM1 to HER2-positive cells allows internalisation of this complex by endocytosis, subsequent intra-lysosomal proteolytic degradation, and then release of potent DM1. a derivative of the antimitotic drug maytansine.[2-6]

1. PI3 kinase inhibitors

P13 kinase is an enzyme important in cell growth. This class has proven efficacy in haematological malignancies. The PlK3CA gene helps control P13 kinase enzyme activity. Some breast cancers have a mutation in the P1K3CA gene (this gene mutation is in the genes of breast cancer, not the person). This mutation can affect P13 kinase and cause the tumour to grow. PI3 kinase inhibitors are a class of drugs designed to interrupt PI3 kinase signals and stop the growth of cancer cells. Buparlisib is under study for the treatment of metastatic breast cancer.[2-6]

1. Targeted therapies against Her-2$_{neu}$ positive Breast cancer:

Figure 1: Time line of HER2- Targeting FDA Approvals in Breast Cancer.[2]

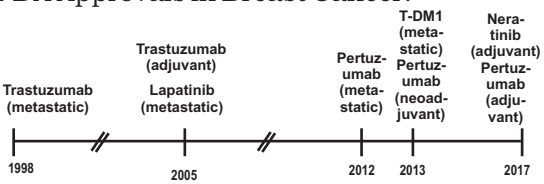

Fig. 1: Time line of HER2- Targeting FDA Approvals in Breast Cancer

The manuscripts with data on Her-2 receptors and their role in breast cancer appear from the late 1980s. Over expression of HER2, which occurs in approximately 20% of breast cancers and largely is because of a specific gene copy number amplification, results in a hyper-proliferative cancer cell and poor prognosis. This single aberrant oncogene becomes such a driving force for growth and proliferation that other usually relevant pathways become irrelevant for growth. This makes HER2 a highly potent therapeutic target. Following are a few drugs that target at the Her-2neu receptor level.[2-3]

- **Trastuzumab**

Trastuzumab, is a humanised monoclonal antibody directed at the

extracellular domain of the transmembrane receptor HER2. Early-phase studies in advanced HER2-positive breast cancer revealed long-term progression-free survivors. Recent advances include validation of subcutaneously injected and biosimilar drugs that expand accessibility and availability of the drug. On the basis of a seminal phase III trial of trastuzumab added to different chemotherapy backbones that revealed great improvement in progression-free survival (PFS) and overall survival despite considerable crossover, trastuzumab was approved by the FDA in 1998 for use in combination with a taxane in the metastatic setting. Subsequent trials established that trastuzumab could be safely and effectively combined with a number of chemotherapy partners, including vinca alkaloids, platinums, and alkylators. Among the subset of dual hormone receptor-positive and HER2-positive cancers, a phase III trial of aromatase inhibition with or without trastuzumab found that these patients did very poorly on antioestrogen alone: PFS was approximately 2 months and was doubled by the addition of trastuzumab, Today, trastuzumab is incorporated with chemotherapy or antioestrogens in the first-line setting and generally, is re-incorporated later with other backbones after ado-trastuzumab emtansine (T-DMD or lapatinib-containing regimens.[2,3,11,13-18]

In neoadjuvant settings the first trials of trastuzumab in HER2-positive breast cancer were reported simultaneously at a special session during the ASCO Annual Meeting in 2005. Trastuzumab demonstrated a relapse-free survival advantage when combined in an anthracyclineltaxane-based regimen in the joint analysis of NCCTG N9831 and NSABP B-31 results and when added after chemotherapy in results from the European study HERA.[15-16] These reports set the standard for incorporation of trastuzumab into treatment of early HER2-positive breast cancer. The results were confirmed and extended by the BCIRGOOB trial. which also found improved outcomes when trastuzumab was added to docetaxel plus carboplatin. Recent updates suggest that trastuzumab with other chemotherapy agents, results in a 40% proportional and nearly 10% absolute overall survival advantage. A simpler regimen of single-agent taxane for 12 weeks with trastuzumab for 1 year was tested in a single-arm trial in patients with low clinical risk and HER2-positive disease; results demonstrated a 98% distant disease-free survival at 3 to 4 years.[2,3,11,13-18]

- **Lapatinib**

Lapatinib is a small-molecule dual Her-2 receptor inhibitor. In the metastatic setting, the drug was approved after a phase III trial in which was added to capecitabine in trastuzumab-pretreated HERZ- positive breast cancer. The PFS showed a 50% improvement. Later studies of lapatinib added to taxanes in the earlier-line setting also suggested improvement in outcome. Lapatinib added to trastuzumab demonstrated improved survival compared with trastuzumab alone in patients who were treated with either 2 or

3 chemotherapy regimens. Added to aromatase inhibitor in dual HR +ve. HER2 +ve breast cancer. lapatinib, like trastuzumab. doubled the baseline PFS seen with aromatase inhibitors alone.[12,14,19,20]

Lapatinib in the adjuvant setting looked promising on the basis of a neoadjuvant study that demonstrated greatly augmented pathologic complete response compared with chemotherapy plus trastuzumab alone. The ALTTO, failed to meet its pre-specified statistical endpoint with a hazard ratio showing only a small advantage of 0.84 in favour of lapatinib. Therefore. lapatinib is not included in neoadjuvant or adiuvant regimens today.[2]

- **Pertuzumab**

Pertuzumab binds to the hetro-dimerisation domain. In the metastatic setting, pertuzumab with trastuzumab plus a taxane in the first-line setting was attempted in the CLEOPATRA trial. The results showed that pertuzumab improved both PFS and overall survival, the latter by an astounding duration: 16 months. The benefit of pertuzumab added to trastuzumab with antioestrogens (called THP) also was demonstrated in the PERTAIN study, in which pertuzumab added 3 months of PFS (HR 0.65) to that of an aromatase inhibitor plus trastuzumab alone.[2,3,17]

NeoSPHERE demonstrated that pertuzumab added to chemotherapy plus trastuzumab significantly increased pathologic complete response in the neo-adjuvant setting. On the basis of these results, the FDA for the first time in 2013 approved pertuzumab. The results of the NeoSPHERE were validated by the results of the APHINITY adjuvant trial. The results showed an event-free survival improvement by the addition of pertuzumab to AC-TH (AC-THP) or to the non-anthracyciine TCH regimen (called TCHP). Pertuzumab may be incorporated into neoadjuvant or adjuvant high-risk settings and given for 1 year concurrent with trastuzumab.[2-6,17]

- **T-DM1**

The antibody-drug conjugate T-DM1 links the tubulin inhibitor emtansine to trastuzumab. which functionally creates a Trojan horse anti-HER2 that spares the toxicity of the free cytotoxic. In the EMILIA trial, T-DM1 alone was compared with capecitabine plus lapatinib. The T-DM1 arm proved superior from an efficacy standpoint with nearly 6-month improvement in overall survival as well as better tolerability. In the first-line setting. the MARIANNE trial found that T-DM1 and T-DM1 plus pertuzumab were no better than a taxane plus trastuzumab. It was concluded that T-DM1 is inferior to the standard first-line metastatic regimen THP but remains a favoured second-line regimen. T-DM1 is now standard second-line therapy in countries where it is affordable and available and it is given alone.[2,3,6,17]

In the neoadjuvant setting, the KRISTINE trial found an inferior pathologic complete response rate to T-DM1 plus pertuzumab compared with TCHP, which suggests that, in this setting also, T-DM1 is inferior to a free cytotoxic plus trastuzumab. Results with T-DM1 in

the adjuvant setting are available, such as KATHERINE (NCT01772472) and are promising.[2]

- **Neratinib**

This is an irreversible HERIIHER2 small molecule inhibitors. In the First-line NEFERT-T trial, neratinib plus paclitaxel showed efficacy similar to that of trastuzumab plus paclitaxel, which suggests inferiority to the standard THP first-line regimen. Central nervous system progression appeared less frequent and occurred later in the neratinib arm of NEFERT-T. Translational Breast Cancer Research Consortium (TBCRC) phase ll trial of single-agent neratinib in progressive central nervous system metastases in HER2-positive disease found an only 8% response rate.[2,3,6]

Due to this the role of neratinib at this time in the metastatic setting is unclear. Neratinib was compared with trastuzumab combined with a taxane and then followed by AC in the adjuvant setting. The results suggested a superiority in the HER2- positive cohort. Especially those patients whose disease was hormone receptor negative.[2] The adjuvant ExteNET trial compared neratinib versus placebo after completion of the year of trastuzumab. The results at 5 years revealed 27% fewer invasive disease-free survival events (absolute difference, 2.5%). in ExteNET the benefit appeared to be driven largely by the HR-positive and node-positive (especially 2 four nodes) subsets. The FDA approved Neratinib for adjuvant use on the basis of these findings in 2017.[2]

Hormonal therapy

History goes back to 19th century where actual targeted therapy started in breast cancer, oophorectomy was used as an intervention by George Thomas Beatson, Dr. Beatson, then a surgeon at Edinburgh University observed that rabbit breasts stopped producing milk after he removed the animals' ovaries: "This fact seemed to me of great interest. for it pointed to one organ holding control over the secretion of another and separate organ." He observed removal of ovaries caused regression of breast lesion. Without knowing about oestrogen, he had discovered that its presence was crucial to the growth of some breast cancers and that removing the ovaries - the main source of oestrogen--was a successful anticancer treatment.

Today we are using hormonal therapy in neoadjuvant /adjuvant and metastatic setting as standard of care. either by blocking oestrogen on breast cancer cells (achieved by selective oestrogen receptor modulators, such as tamoxifen) or by deprivation/elimination of circulating oestrogen (achieved by aromatase inhibitors and ovarian suppression therapy or oophorectomy). These approaches have been the mainstay of therapy for OR-positive and progesterone receptor-positive cancers for decades and remain so today.

With sequential use of various hormonal therapies it's possible to extend survival. Hormonal resistance has always been an issue and to some extent with extensive research hormone resistance can be addressed with use of mTOR inhibitors and CDK inhibitors which are

available for use in India.

Hormonal therapy in adjuvant setting in general used for 5 to 10 years based on aggressive biology of disease (Decided by clinical factors such as patient's age, node positivity, grade and size of tumour, molecular signature of breast cancer).

For premenopausal patients tamoxifen is being used. For postmenopausal patients aromatase inhibitor is used. These are oral agents and associated with typical side effects which are manageable. Adherence to treatment is important for successful outcome of breast cancer.[21-23]

Chemotherapy and endocrine therapy are still the basic treatments, although optimisation of dosage remains an unmet need. Depending on the receptor status, patients' demand and physician's preference, the drug therapy for advanced and metastatic breast cancer varies from patient to patient. For breast cancer conventional treatments fail, immunotherapy based on check point inhibitors is promising, especially when combined with chemotherapy. None the less, these therapies, be it targeted therapies, immunotherapies or chemotherapy drugs, are a *"New hope for Breast Cancer Patients!"*

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Non-specific low back pain

Non-specific low back pain affects people of all ages and is a leading contributor to disease burden worldwide. Management guidelines endorse triage to identify the rare cases of low back pain that are caused by medically serious pathology, and so require diagnostic work-up or specialist referral, or both. Because non-specific low back pain does not have a known pathoanatomical cause, treatment focusses on reducing pain and its consequences. Management consists of education and reassurance, analgesic medicines, non-pharmacological therapies, and timely review. The clinical course of low back pain is often favourable, thus many patients require little if any formal medical care.

Low back pain is a symptom rather than a disease. Like other symptoms, such as headache and dizziness, it can have many causes. The most common form of low back pain is non-specific low back pain. This term is used when the pathoanatomical cause of the pain cannot be determined.

Diagnostic investigations have a role when the clinician suspects a specific disease process that would be managed differently from non-specific low back pain.

The American College of Physicians' guideline for diagnostic imaging suggests immediate imaging when there are major risk factors for cancer, risk factors for spinal infection or cauda equina syndrome, or severe neurological deficits. By contrast, these guidelines advise deferral of imaging pending a trial of therapy when there are weaker risk factors for cancer or risk factors for spondyloarthritis, vertebral compression fracture, radiculopathy, or spinal stenosis.

72% of patients with acute low back pain had completely recovered by 12 months, whereas 42% of those with persistent low back pain recovered within 12 months.

A review of 17 systematic reviews of the prognosis of low back pain reported that the following factors were consistently associated with poor outcome: higher disability, presence of sciatica, older age, poor general health, increased psychological or psychosocial distress, negative cognitive characteristics, poor relationships with colleagues, heavy physical work demands, and presence of compensation.

Chris Maher, Martin Underwood, Rachelle Buchbinder, The Lancet, Feb 2017, Vol 389, 736-739