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Recent advancements in the treatment of breast cancer

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ABSTRACT

The greatest cause of cancer death among women today and cancer that is most usually identified as being life-threatening in women is breast cancer. Research on breast cancer over the past 20 years has significantly advanced our understanding of the condition and produced more effective, less harmful treatments. Early diagnosis at stages amenable to complete surgical resection and curative therapy has been made possible by increased public awareness and enhanced screening. As a result, breast cancer survival rates have considerably increased, especially for younger women. This page discusses the different forms, causes, clinical symptoms, and approaches for treating breast cancer that is both non-drug (such as surgery and radiation) and drug-based (such as chemotherapy, gene therapy, etc.).

Key words: breast cancer, tumour, chemotherapy, gene therapy

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INTRODUCTION

Breast cancer is the most common cancer among women, accounting for more than one in ten new cancer diagnoses each year. The breast is made up of a variety of tissues, and among these tissues is a network of lobes, each of which is made up of milk gland-containing little tube-like structures called lobules. The milk is transported from the lobes to the nipple via tiny ducts that connect the glands, lobules, and lobes. Additionally, the breast tissues include blood and lymphatic vessels. Healthy cells in the breast begin to proliferate uncontrollably to form tumours, which can be malignant or benign. Malignant cancers are those that spread to various bodily areas, whereas benign cancers can grow but do not spread [1]. Cancer cells often go undetected if the immune system is weakened or if the number of mutated cells is too great for the immune system to eliminate; this is brought on by many factors including a toxic environment (exposure to radiation, pollutants), a poor diet, a genetic predisposition [2], and old age (people 80 years and older) [3]. Early detection and a resulting decline in the risk of death have improved, especially in younger women, as a result of greater public awareness and innovative screening techniques. The many types of breast cancer, treatment options for breast tumours that are triple-negative, HER2-positive, and both, as well as the potential benefits of combinatorial therapy for the treatment of breast cancer in the future, will all be covered in this review.

LITERATURE REVIEW

Breast cancer

The second-leading cause of cancer death among American women is breast cancer, which is cancer that is most frequently diagnosed. In the United States, it is predicted that 1 in 8 women who are living now will develop breast cancer at some point in their lives. According to 40,000 women will die from breast cancer in 2014 and an estimated 232,670 women will be diagnosed with the disease [4]. Concerning including all races combined, the age-adjusted incidence rate from The Surveillance, Epidemiology, and results of the National Cancer Institute. The program's 18 geographic regions were 123.8 per 100,000 women per year; however, the highest rates were noted for whites (127.4 per 100,000) and African Americans (121.4 per 100,000), and the lowest rate was noted among American Indian/Alaska Natives (77.1 per 100,000). The fatality rate among all racial/ethnic groups was highest among African American women, 30.8 per 100,000, although they had a lower incidence rate than white

women [5]. The later stage upon diagnosis, the more aggressive tumours, the discrepancies in adjuvant treatment, and the greater mortality rate are potential contributing factors.

TYPES OF BREAST CANCER

According to three classifications-tumour grade, morphological classification, and m olecular c lassification-breast ɑ ncer is incredibly diverse [6].

The most t ypical is t he morphological classification, which distinguishes between the morphological characteristics of the tumour and normal cells. This classification is also referred to as the Nottingham Prognosis index and is very crucial for prognosis, with its reproducibility being a major problem. Breast cancer's invasiveness and its source are the two main morphological categories [7].

Non-invasive breast cancer

Cancer cells stay in the ducts and do not spread to the fatty or breast tissues around them. 90% of non-invasive breast cancers are lobular carcinoma in situ, which is thought to be a marker indicating a higher risk of breast cancer growth in the future. However, some non-invasive breast cancers are ductal carcinoma in situ. It should be noted that the phrase "in situ" denotes that cancer did not spread from its original location.

Invasive breast cancer

Cancer cells invade the adipose and breast tissues after crossing the ductal and lobular walls. Cancer spread to other organs without necessarily being invasive.

Invasive ductal carcinoma

It represents 80% of cases of breast cancer. It initially begins in the ducts and then spreads via the breast cancer tissues nearby, with the potential to migrate to other body areas.

Medullary carcinoma

Accounts for 5% of breast cancer diagnoses that can be distinguished between tumour and normal tissue.

Mutinous carcinoma

This extremely uncommon kind of breast cancer is created by the cancer cells that produce mucus.

Inflammatory breast cancer

It is extremely uncommon, making up about 1% of all occurrences of breast cancer, yet it is expanding quickly. In this form, cancer cells obstruct the lymphatic capillaries, resulting in breast irritation and the development of thick ridges.

Paget's disease of the nipples

Only 1% of cases of breast cancer are diagnosed because of milk ducts that extend into the areola and nipple [1].

Breast cancer is classified molecularly into two subgroups

Oestrogen restrogeositive and oestrogen receptor-negative regarding its molecular classification breast cancer is divided into two subcategories estrogen receptor-positive and estrogen receptor-negative.

In addition to these subcategories, triple-negative breast cancer is also noteworthy. This type of breast cancer lacks immune histochemical evidence of progesterone, oestrogen, or Human Epidermal Receptor 2 (HER2) [8].

DIFFERENT TREATMENTS FOR BREAST CANCER

Breast-conserving therapy

BCT entails lumpectomy, the removal of the tumour, and adjuvant Whole-Breast Irradiation (WBI). The breast must be suitable for a follow-up to enable quick diagnosis of local recurrence, patients must be able to undergo radiotherapy, and the tumour must be excisable to negative margins with an acceptable cosmetic outcome to do BCT. These prerequisites logically lead to the limitations of BCT. Diffuse suspicious or malignant-appearing calcifications, the disease that cannot be resected to negative margins with satisfactory cosmetic results, and the presence of conditions that make radiation delivery impossible, such as active scleroderma or prior treatment of the breast field, are all contraindications to BCT. [9] "No ink on the tumour" is the definition of a negative margin. [10] More extensive clear margins are not necessary for BCT and do not improve local control in invasive breast cancer, according to [11]. No matter the size of the tumour, a lumpectomy can be performed if negative margins can be reached with a respectable cosmetic result. Neo-Adjuvant Chemotherapy (NAC) can be used to downstage tumours in women with big tumours in comparison to their breast size (see later discussion). BCT is not contraindicated in cases of young age, aggressive tumour subtype (HER2-positive and triple-negative), or lobular histology. A bilateral mastectomy is an option for patients with BRCA1/2 mutations because the risk of developing new primary breast cancer in the 20 years after diagnosis can vary from 26% to 40% depending on the age at which the first cancer appeared, whether oophorectomy was performed and whether endocrine therapy was used [12].

Despite this increased risk, a BRCA mutation does not automatically rule out breast conservation; patient preference must also be taken into account. The imaging modalities that are typically used to choose patients for BCT include physical examinations, mammography, and diagnostic ultrasound. 88% of women who attempted BCT successfully underwent the operation in a population-based trial of 1984 women with ductal carcinoma in situ and stage I and stage II invasive malignancies [13].

There is debate over the utility of MR imaging before surgery. According to a meta-analysis by [14], MR imaging is more sensitive than mammography or ultrasound in identifying extra illness in 16% of patients. It was though illnesses MR imaging would enhance lumpectomy candidate selection and lower reoperation rates. However, numerous studies of preoperative MR imaging have shown an increase in the rates of both contralateral preventive mastectomy and ipsilateral mastectomy for the index tumour without a corresponding decline in immoderation and recurrence rates [15].

Preoperative MR imaging and surgical outcomes were compared in a systematic evaluation including 85,975 individuals. After

controlling for patient age, MR imaging was linked to an increased risk of ipsilateral prophylactic mastectomy (OR 1.39; 95% Confidence Interval (CI) 1.23-1.57; P .001) and contralateral prophylactic mastectomy (OR 1.9; 95% Confidence Interval (CI) 1.25-2.91; P 5.003). The rate of positive margins, reoperation, or re-excision was not significantly decre-excision preoperative MR imaging. Additionally, no differences were seen between patients chosen with and without MR imaging in a patient-level meta-analysis assessing the effect of MR imaging on local recurrence rates following BCT [16]

The knowledge that local recurrence is influenced not only by tumour load but also by tumour biology and the use of efficient adjuvant systemic therapy is consistent with the inability of the diagnosis of subclinical illness using MR imaging to translate into improved local recurrence outcomes. Preoperative MR imaging is not recommended for routine use in the absence of a specific clinical question. Preoperative MR imaging may be particularly helpful in cases of mammographically and/or sonographically occult tumours, Paget disease, determining the extent of residual disease in patients who want to preserve their organs after NAC, and when there are notable differences between physical examination, mammography, and ultrasound measurements of tumour size [16].

Adjuvant radiation in breast-conserving therapy

Before surgery, it's critical to ascertain whether or not a patient qualifies for adjuvant radiotherapy. Radiation therapy may not be recommended in cases of prior chest wall irradiation, pregnancy at the time of diagnosis, and connective tissue/collagen vascular disorders. If the radiation threshold dosage was surpassed during earlier therapy, patients with a history of mantle radiation for Hodgkin lymphoma could not be eligible for adjuvant radiotherapy. Radiation delivery is not advised during any trimester of pregnancy. But if a woman develops invasive breast cancer in the second or third trimester, a lumpectomy can be done, and adjuvant chemotherapy can be given before breast irradiation is given after childbirth. Mastectomy is the recommended treatment when breast cancer is discovered during the first trimester and adjuvant chemotherapy is not indicated. Scleroderma, Sjogren syndrome, systemic lupus erythematosus, and dermatomyositis polymyositis are among the connective tissue/collagen vascular disorders that are considered relative contraindications to the delivery of breast irradiation due to small retrospective studies that suggest an increased incidence of acute and late radiation toxicities in these patients. Matching case-control studies haven't consistently shown an increase in risk, except for scleroderma. However, these were extremely small retrospective studies, and it's possible that patients with severe disease weren't chosen for radiation [17]. In these patients, preoperative radiation oncology consultation is necessary. After a lumpectomy, WBI is administered to remove any microscopic illness that might have persisted in the breast even with negative margins. Holland and associates detected additional tumour foci within 2 cm of the index tumour in 56 (20%) cases and greater than 2 cm from the index cancer in 121 (43%) cases in pathologic investigations of mastectomy specimens in 282 individuals with clinical and mammographically unifocal breast malignancies. Adjuvant radiation therapy reduces local failure rates after lumpectomy by around 50% and improves breast cancer-specific survival. 2-4,6 A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) of 17 randomised trials involving 10,801 women who underwent BCT showed that radiation therapy reduced the risk of any recurrence from 35.0% to 19.3% at 10 years and the risk of breast cancer death from 3.8% (95% CI 1.6-6.0, P 5.00005) at 15 years. Researchers infer that there is an equivalent avoidance of 1 breast cancer mortality after 15 years for every 4 recurrences that are averted at 10 years [18].

The delivery of standard WBI using 50 Gy in 25 parts, daily, over roughly 5 to 7 weeks was the subject of the data, which was then followed by an additional boost of roughly 10 Gy to the tumour bed. Hypo-fractionated WBI allows for treatment completion in about three weeks and lowers the number of treatments required by administering a bigger fraction over a shorter amount of time. Randomized trials found comparable local recurrence rates at 5 years and 10 years, no difference in overall survival, and better cosmetic results than with standard fractionation [19]. Radiation is applied to a small portion of breast tissue concentrated around the tumour cavity during Partial Breast Irradiation (PBI). PBI can be administered via a variety of methods, such as intraoperative irradiation, interstitial or intracavitary brachytherapy, or conventional external beam therapy. PBI may be advantageous since it takes less time to complete and only irradiates a part of the breast, perhaps enabling repeat BCT if a new main tumour appears. Trials are currently being conducted to determine whether or whether PBI is equally effective in terms of local control, survival, and cosmesis as standard or hypofractionated WBI. It has not been possible to identify a subgroup of BCT patients who do not respond well to radiotherapy using traditional tumour pathologic characteristics. But in older postmenopausal women with tiny oestrogen receptor-positive tumours undergoing adjuvant endocrine therapy, 2 prospective randomised studies showed adequate local control rates without radiation [20]. Candidates for this strategy are elderly women (70 years and older) with stage I oestrogen receptor-positive breast cancer who will receive endocrine therapy.

Numerous studies have demonstrated an improvement in quality of life after BCT, greater cosmetic satisfaction with BCT in comparison to mastectomy without reconstruction, and comparable satisfaction in comparison to mastectomy with rapid reconstruction. [21] Theamount of tissue removed has the greatest impact on the cosmetic outcome of BCT; when more than 20% of the breast volume is removed, a cosmetically significant deformity is more likely [22]. Only a small percentage of individuals require such significant resections because the current guidelines do not call for margins larger than no tumour on ink. In these situations, an oncoplastic surgery might be employed to enhance the aesthetic results. By filling in the lumpectomy defect using mastopexy techniques and plastic surgery tissue rearrangement, oncoplastic procedures enhance the shape of the breast that has been preserved. Planning radiation treatments might be challenging since the tumour bed is frequently displaced as a result of the parenchymal rearrangement. To guarantee precise cavity localization during radiation therapy, surgical clips are routinely placed to indicate the lumpectomy cavity's boundaries before tissue rearrangement. Except for fat necrosis, which is higher in oncoplastic treatments (10% vs 25%), small retrospective series of patients undergoing extensive resections report higher patient satisfaction with cosmesis and comparable morbidity and recurrence rates as standard BCT [23, 24].

Mastectomy

The majority of patients who need a mastectomy have the option of a total mastectomy (simple mastectomy), a skin-sparing mastectomy, or a nipple areolar-sparing mastectomy. The chest wall's extra skin, nipple-areolar complex, and breast parenchyma are all removed during a total mastectomy, leaving just enough skin to cover the incision. When patients won't undergo immediate reconstruction, it is typically used. The skin-sparing mastectomy was created to enable prompt reconstruction. It involves the removal of the nipple-areolar complex and breast parenchyma, leaving the skin as a natural envelope for the implantation of a tissue expander/implant or an autologous flap. The skin-sparing mastectomy is oncologic safe, with local recurrence rates of about 6%, comparable to those seen with the conventional simple mastectomy [25, 26].

The nipple areolar-sparing mastectomy, which originally served largely as a preventative measure but is now increasingly employed in patients with invasive cancer, maintains the nipple-areolar complex in addition to the skin envelope. According to reports, local recurrence rates ranged from 2% to 5%, with a median follow-up of 2 years to 5 years [27, 28].

Since the majority of these data come from single-institution retrospective studies with constrained follow-up, patients should be cautiously chosen for this therapy until long-term oncologic safety has been proven. Although eligibility requirements differ by institution, the authors advise restricting this procedure to patients with tumours that are less than 3 cm in size and that are at least 1 cm away from the nipple and do not have significant calcifications that could indicate a significant intraductal component.

Neoadjuvant chemotherapy

Initially, NAC was used to treat locally advanced, incurable breast cancer. To facilitate breast conservation and, in some cases, avoid ALND, NAC has more recently been utilised in operable tumours to downstage disease in the breast and axilla. Several randomised trials have investigated the oncologic safety and equal survival outcomes of NAC [29, 30].

There were no changes in survival or LRR between patients treated with NAC and those treated with surgery followed by chemotherapy, and the number of mastectomy procedures was 17% lower in those getting NAC, according to a meta-analysis [31]. Since many of the women involved in these studies were candidates for BCT upon presentation and so could not benefit from NAC, 17% is a low estimate. When a woman has breast cancer that is unicentric, or enormous with the size of her breast, or when her cancer is triple-negative or HER2-positive, NAC is most likely to permit BCT. It can be difficult to accurately assess a patient's reaction to treatment and the viability of BCT. Although normal MR imaging does not rule out the presence of dispersed foci of viable carcinoma, which may limit BCT, MR imaging is more accurate than mammography or ultrasound in predicting the degree of residual illness [21]. Given that calcifications present at diagnosis rarely disappear with NAC, a mammography is an additional tool to MR imaging in determining if a patient is a good candidate for BCT after NAC. After neoadjuvant therapy, calcifications may also become visible when breast densities associated with the tumour have disappeared or as a result of tumour cell death. According to Feliciano Y, et al. (2017) [32], loss of enhancement on MR imaging does not always mean that calcifications are benign or caused by dead cancer cells, and excision of any remaining palpable masses or radiographic anomalies is usual. It should be noted that a pathologic full response is not necessary for a successful BCT after NAC, nor does the lumpectomy specimen necessitate the removal of the entire volume that the tumour initially filled. Any remaining clinical or imaging problems, or, in the event of a clinical and radiographic full response, excision of the marker at the tumour site and a sizeable sample of nearby breast tissue, should be included in the lumpectomy. Clinically node-negative women who get NAC had a much lower incidence of axillary metastases, and sentinel lymph node biopsy is routine in this population following NAC administration [33, 34]. Increased rates of pathologic complete response with NAC in the breast and axilla are the result of more efficient systemic regimens. The accuracy of sentinel node biopsy following NAC in patients presenting with nodal metastases has been investigated in three prospective randomised clinical studies. According to the ACOSOG Z1071 and SENTINA (Sentinel Neoadjuvant) studies, false-negative rates are less than 10% when dual-tracer mapping is used and three or more sentinel nodes are identified as being negative, which is comparable to what is accepted for sentinel node biopsy in the primary surgical setting. A nodal pathologic complete response and three or more discernible sentinel nodes were found in 48% of 288 patients who initially had nodal metastases and later developed clinically negative nodes after NAC, according to a prospective study from the Memorial Sloan Kettering Cancer Centre [35]. This allowed them to avoid axillary dissection. Completion of ALND is typical in patients who continue to have node-positive nodes. The Alliance A011202 trial is now investigating whether axillary radiotherapy can replace a complete ALND in the case of a positive axillary sentinel node following NAC.

Adjuvant medical therapies for breast cancer

Patients frequently get adjuvant systemic therapy following surgical resection of the primary breast cancer to cure clinically and radiographically occult micrometastatic illness that, if unchecked, could progress to frank metastatic disease. Based on patient risk classification, adjuvant systemic treatments are chosen. Risk is influenced by two factors: the disease burden (number of lymph nodes, size of the primary tumour), and the biology of the illness as indicated by HR and HER2 status and genomic assays. Although individuals with triple-negative and HER2-positive tumours are typically regarded as high risk, those with HR-positive, HER2-negative tumours have a wide range of biological characteristics. Chemotherapy has been the standard for healthy women in this group based on trials showing a small but statistically significant benefit for the treatment of HR-positive, HER2-negative, and node-negative breast cancers with chemotherapy in addition to endocrine therapy [36]. Commercially accessible genomic assays look for genes associated with cancer in DNA obtained from tumours to assess the risk of recurrence and potential benefits of chemotherapy. Clinicians now have more information on which patients should undergo chemotherapy thanks to these commercially available diagnostics.

Chemotherapy

Systemic chemotherapy is often advised for patients at high

risk. There are numerous types of conventional chemotherapy available, most of which include both an anthracycline and a taxane. Doxorubicin and cyclophosphamide for 4 cycles, then paclitaxel for 4 cycles (AC-T) is a typical regimen used in the US. It is preferable to administer dose-dense AC-T every two weeks with growth factor support following each chemotherapy cycle [37]. Other recommended AC regimens include weekly paclitaxel for 12 weeks or every three weeks for 4 cycles of docetaxel [38]. Docetaxel with AC (DAC) is another common choice, however, it is not better than the aforementioned regimens because docetaxel has higher febrile neutropenia rates than paclitaxel and is more hazardous overall [39]. Adjuvant chemotherapy is beneficial in lowering breast cancer mortality and recurrence, with a greater magnitude of effect in individuals with HR-negative illness Berry and colleagues [40]. Chemotherapy reduced Relative Risks (RR) by 21% to 25% in patients with HR-negative cancer, compared with an 8% to 12% RR decrease in individuals with HR-positive cancer, according to the analysis of trial data from the Cancer and Leukaemia Group B and US Breast Cancer Intergroup. The Oncotype DX genomic assay provides an estimate of chemotherapy benefit for patients with HR-positive, node-negative breast cancer; patients with high Oncotype recurrence scores have a significant reduction in risk of recurrence with chemotherapy (RR 0.26), whereas those with low scores derive little to no benefit from chemotherapy [41]. In the absence of the results of the Trial Assigning Individualized Options for Therapy, there is insufficient data to make a unified recommendation regarding the adjuvant treatment of patients with intermediate-risk Oncotype recurrence scores (TAILORx trial). Patients were randomly assigned in this study to receive either endocrine therapy alone or endocrine therapy plus chemotherapy if their Oncotype recurrence scores ranged from 11 to 25. Patients in this group may receive anthracycline-containing or anthracycline-sparing chemotherapy regimens. Endocrine therapy alone is sufficient for patients with low Oncotype recurrence scores, especially scores under 11. With endocrine therapy alone, these patients had a fantastic prognosis, with a 5-year overall survival rate of 98% [42]. Because node-positive breast cancer patients have a worse prognosis than node-negative breast cancer patients, chemotherapy is typically advised for these individuals. Some retrospective investigations have questioned the validity of this advice. In the South-West Oncology Group (SWOG) 8814 research, Albain and colleagues98 found no benefit from chemotherapy in patients with HR-positive, lymph node-positive breast cancer and a low Oncotype recurrence score. The Rx for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER) trial, which enrolled patients with HR-positive breast cancer and 1 to 3 positive nodes and Oncotype recurrence scores of 25 or less, was created in response to this discovery and gave them normal endocrine therapy while randomly assigning some to chemotherapy and others to none. Depending on the findings of this investigation, chemotherapy may or may not be avoided for some individuals with the node-positive illness.

THE INTEGRATION OF NANOTECHNOLOGY IN BREAST CANCER TREATMENT

Nanoparticles

Anti-cancer medications, as previously mentioned, frequently have harmful side effects since they are hydrophobic, untargeted, and toxic [43]. A larger concentration of medicine will target malignant cells using nanotechnology because it has fewer adverse effects due to the restriction on drug degradation [44]. Additionally, it hunts out and destroys breast cancer stem cells, a significant contributor to chemotherapy resistance [45]. This method involves incorporating a nanoparticle into the anti-cancer medication. The U.S. Food and Drug Administration (FDA) has authorised numerous nanoparticle-based anti-cancer medications, and many more are still in the testing phase.

Liposome based nanoparticles

Hydrophobic drugs, which make up the majority of anti-cancer drugs, can be incorporated into the lipid layer of liposomes while hydrophilic drugs are located in the core. This will lessen the toxic effects of these drugs and increase their circulation time. Liposomes are made up of an aqueous heart and a membrane lipid layer. Additionally, liposomes are bioconjugated with selective ligands like antibodies, aptamers, etc. to increase their selectivity to malignant cells.

Doxil®, the first lysosome-based medication to receive FDA approval, intercalates between DNA base pairs, inhibiting transcription while also causing DNA synthesis [46].

Polymeric nanoparticles

The hydrophobic anti-cancer medicine is enclosed inside the polymer nanoparticles' core, which is similar to liposomes but not the same, and the hydrophilic anti-cancer drug is bound to the polymer's outer shell via covalent, electrostatic, etc. bonding. Peptides and antibodies are linked to the polymers to target cancer cells specifically [47]. According to Tang X, et al. (2017) [46], polymers are stable regardless of temperature, pH, external stimuli, etc. When compared to conventional chemotherapy (175 mg/m^2), Phase II trials have shown that Genexol®-PM can administer the antimitotic drug Paclitaxel at a larger dose (300 mg/m^2) with less toxicity [48, 49].

Nab paclitaxel

One of the first medications for the treatment of breast cancer to receive FDA approval is paclitaxel. The medicine is taken along with Cremophor EL, a member of the taxane family that has poor water solubility and induces severe dose-dependent toxicity that may result in death. The FDA has developed and authorised Nab-Paclitaxel to restrict its use. Under high pressure, albumin, a transporter of hydrophobic molecules, was reversibly linked to paclitaxel to create this medication. Nab paclitaxel made it possible to use Paclitaxel safely at significantly greater doses without experiencing any negative side effects [46].

Gene therapy

Gene therapy for cancer, such as oncogene inactivation and tumour suppressor genes, has become more popular as a result of the fact that many malignancies are caused by complicated changes in the genes [47].

Oncogene inactivation:

Numerous oncogenes, such as ErB2 (Erb-B2 Receptor Tyrosine Kinase 2) and PIK3CA (phosphatidylinositol-4,5-bisphosphate

3-kinase catalytic subunit alpha), are linked to various cancers, including breast cancer. The most frequently used technique for inactivating oncogenes de clinical studies is antisense. Additionally, adenoviral gene inhibition of ErB2 oncogene transcription is a particularly effective method for malignancies that exhibit this oncogene, such as breast cancer.

Tumour suppressor gene augmentation:

Adenoviral vectors have been used in numerous trials to attempt and increase the quantity of p53 since mutations in many tumour suppressor genes have been linked to various types of cancer. Furthermore, the BRAC1 breast cancer gene is being inserted into ovarian cancer using viral vectors. Them utant g ene's overwhelming influence on the normal gene, however, could cause these strategies to fail [47].

Targeted therapies for endocrine therapy

Resistance Phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), and mammalian target of rapamycin (mTOR) complexes are the three protein components that make up the PAM pathway, which is involved in cell growth, survival, and proliferation. Targeting the PAM pathway in cancer therapy has received a lot of investigation since endocrine therapy resistance in endocrine-resistant breast tumours is correlated with greater PAM pathway activation. A regulatory p85 subunit and a catalytic p110 subunit make up the heterodimer PI3K, which has two subunits altogether. The p hosphorylated t yrosine r esidues s erve a s t he p 85 s ubunit's docking location upon stimulation of the Receptor Tyrosine Kinase (RTK). Ras proteins then recruit and activate the p110 subunit, which results in the conversion of phosphatidylinositol-4,5-biphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3). Them TORC1 and m TORC2 complexes are then activated as a result of the subsequent phosphorylation of the serine/threonine kinase, Akt. According to Paplomata E, et al. (2014) [48], MTOR activation boosts protein synthesis, which is essential for cell growth and proliferation. Even in the presence of endocrine therapy, activating PI3K mutations and/or abnormal signalling in the absence of growth factors may promote the survival of breast cancer.

mTOR inhibitors:

Everolimus, an mTOR inhibitor, was first approved in 2009 for the treatment of advanced renal cell carcinoma and the avoidance of kidney transplant rejection in 2010 [49]. After researching the efficacy of an everolimus-exemestane (an AI) combination in treating HR-positive, HER2-negative metastatic breast cancer, the US Food and Drug Administration (FDA) approved this pharmaceutical regimen in 2012 for postmenopausal women who met the conditions. Everolimus inhibits further "cell cycle progression, cell growth, and proliferation" by connecting to mTOR via the FK506-binding protein 12 receptor [50]. The effectiveness of everolimus-tamoxifen (a SERM) co-treatment in postmenopausal women with locally advanced/metastatic, HR-positive, HER2-negative, AI-resistant breast cancer is being examined in more clinical studies. According to these investigations, patients with secondary endocrine resistance may experience therapeutic advantages [51]. Similar to everolimus, temsirolimus is another mTOR inhibitor that the FDA approved as a treatment for advanced renal cell carcinoma in 2007 [52]. Temsirolimus binds to FK506-binding protein as well, and the resultant complex attaches to mTOR to inhibit its impact on the cell cycle. progression through the cell development and proliferation during the G1 phase. Early clinical research primarily evaluates the efficacy of single-agent temsirolimus in advanced or metastatic breast tumours that are ER-positive, HER2-positive, or PTEN-deficient [53, 54]. In patients with local A phase, 2 clinical study employing intermittent temsirolimus in combination with chemotherapy is being conducted for advanced/metastatic breast cancer. therapy with daily letrozole, an AI, demonstrated a higher when letrozole is used alone, the median Progression-Free Survival (PFS) rate is lower. A similar treatment plan was assessed in a subsequent phase 3 clinical research on patients with HR-positive, locally progressed or metastatic breast cancer who had never taken aromatase inhibitors before. Although the PFS was higher in patients under 65 than in those over 65 in this study's subgroup analysis, there was no discernible clinical benefit, suggesting that younger postmenopausal breast cancer patients may benefit from the use of temsirolimus-letrozole combination therapy [51]. Using sirolimus to prevent organ rejection in recipients of kidney transplants has also been given FDA approval [49]. The efficiency and security of a dual-drug regimen of sirolimus and tamoxifen in HR-positive, and HER2-negative metastatic breast cancer are being investigated in phase 2 clinical trials. According to preliminary data, patients who received the medication combination had a higher rate of progression-free survival than those who had received tamoxifen alone [51].

PI3K inhibitors:

In May 2019, the FDA approved the use of alpelisib (BYL719), a -specific PI3K inhibitor, for the treatment of postmenopausal patients with metastatic or advanced breast cancer who test positive for HR but negative for HER2. Patients who have mutations in the PIK3CA gene that activate the enzyme often receive it in addition to the SERD fulvestrant. Increased cell growth and proliferation are brought on by the PIK3CA mutations, which cause the PI3K p110 subunit alpha isoform to become hyperactivated. In contrast to the use of either alpelisib or fulvestrant as monotherapies, Higher PFS was achieved in patients receiving alpelisib-fulvestrant combination therapy due to the anticancer activity's synergistic effects and the SOLAR-1 and BYLieve clinical trials [55, 56]. Targeted therapy with alpelisib and fulvestrant is effective, especially for cancers with endocrine resistance. endocrine resistance because the PIK3CA mutation is present in 40% of individuals with HR-positive, HER2-negative breast cancer. [57]. Taselisib (GDC-0032) is a selective class I PI3K inhibitor that doesn't affect the beta isoform of the p110 subunit. Along with inhibiting PI3K downstream signalling, it also causes the levels of the mutant p110 subunit to drop. It is thought to be less toxic and more effective than pan-class I PI3K inhibitors because it spares the p110 subunit [58]. Taselisib's effectiveness and safety in the treatment of advanced breast cancer are being investigated in ongoing clinical trials. In phase 3 randomised study SANDPIPER, fulvestrant alone and taselisib combination therapy are compared for their clinical efficacy in treating advanced or metastatic breast cancer. therapy to fulvestrant alone in the treatment of advanced or metastatic breast cancer that is ER-positive, HER2-negative, and PIK3CA mutant [59]. Taselisib's clinical actionability in PIK3CA-mutant breast tumours was assessed in a phase 1 basket research, but the findings

indicated minimal clinical action ability of single-agent taselisib therapy. Additionally, a phase 1b trial is currently being conducted to ascertain the maximum taselisib dose that can be safely used by examining the safety of taselisib combination therapy in a dose-dependent manner with additional anti-HER2 drugs [58]. An oral pan-class I PI3K inhibitor called pictilisib (GDC-0941) is currently undergoing clinical studies to treat advanced breast cancer. When pictilisib binds to the Adenosine Tri Phosphate (ATP)-binding pocket, it non-specifically inhibits all four isoforms of PI3K, including the alpha, beta, delta, and gamma subunits. Additionally, both PIK3CA-mutated and HER2-positive and -negative tumours were successfully treated with it. Pictilisib medication was associated with increased "antitumor activity of taxanes" and apoptosis, according to preclinical investigations. A monoclonal antibody called trastuzumab is used to treat HER2-positive breast cancer. malignancies and pictilisib treatment combined were shown to synergistically reduce cell proliferation in HER2-positive tumours. Due to the observed growth suppression when given to activated human endothelial cells, pictilisib may also have antiangiogenic properties. However, because of its non-isoform-specific activities on PI3K, which might result in unexpected toxicities, safety has been a significant worry. Another pan-class I PI3K inhibitor that is orally accessible and undergoing early-phase clinical research is buparlisib (BKM120). Clinical trials are assessing buparlisib's effectiveness and safety in the treatment of endocrine-resistant metastatic breast tumours, just like they do with other PI3K inhibitors. A phase 2 research that assessed the effectiveness of buparlisib as a single-agent therapy for metastatic TNBC found no statistically meaningful prolongation of survival. Altered mood, rash, and hyperglycaemia are examples of dose-limited toxicities because it is a pan-class PI3K inhibitor, "highlighting the pharmacological constraints of pan-PI3K inhibition".

PTEN upregulation:

PTEN tumour suppression is either reduced or absent, especially in more aggressive tumours, which promotes unchecked cell growth and proliferation. PTEN is a natural inhibitor of the PAM pathway, hence the CRISPR/dCas9 system was used to stimulate PTEN tumour suppressor expression in TNBC to find a potential therapeutic strategy. According to a study CRISPR/dCas9-induced, PTEN expression in the TNBC cell line SUM159 significantly inhibited the PAM pathway's downstream signalling. Lower levels of phosphorylated Akt and mTOR were seen when PTEN expression was activated, indicating an inhibitory influence on subsequent oncogenic signalling. Studies are being conducted on natural chemicals that have the potential to be anticancer agents in addition to using gene editing. Bergapten, a polar derivative, was applied to the breast cancer cell lines MCF-7 and ZR75-1 to assess its anti-survival effects. The stimulation of autophagy and enhanced PTEN expression were both seen in the results. Bergapten treatment may play a role in triggering breast cancer cell death as the activated autophagy phenotype may increase vulnerability to cell death. In a different study, Wu et al. found that oridonin, a Chinese herbal extract, overexpressed PTEN, which resulted in a decrease in cell proliferation and an increase in apoptosis in human colon cancer cells. After receiving oridonin therapy, it was shown that the PTEN protein levels in these colon cancer cells had grown. Although this work focused on colon cancer cells, the findings suggest that boosting PTEN expression in breast cancer cells may also have anticancer potential. These results point to a potentially fruitful approach for PTEN upregulation in upcoming cancer therapies. Off-target toxicities will be considerably decreased, especially with the accuracy of the CRISPR/Cas9 technology. Due to the growing acceptance of combination therapy, the use of the CRISPR/Cas9 system in addition to current breast cancer therapies including chemotherapy, hormone therapy, and/or radiation therapy may also result in greater efficacy and less drug therapy.

LKB1-AMPK:

Activation AMP-activated protein kinase, a tumour suppressor, is phosphorylated and activated by liver kinase B1, a serine/threonine kinase. The mTOR pathway is therefore negatively regulated by activated AMPK, stopping future cell growth and metabolism. Additionally, Transforming Growth Factor beta (TGF-β) synthesis and signalling are inhibited by activated AMPK. In the early phases of carcinogenesis, TGF- exerts inhibitory effects, but as the process progresses and metastasizes, it "promotes tumour development and metastasis". TGF- promotes the epithelial-to-mesenchymal transition, which increases the cell's ability to move, migrate, and break down the extracellular matrix. This is one significant way that TGF- promotes metastasis. Because active AMPK can reduce TGF- signalling, this has major implications for AMPK activation as a potential therapeutic target for cancer treatment. One such substance that does this is honokiol, which phosphorylates LKB1 and activates AMPK. A naturally occurring small-molecule polyphenol called honokiol was discovered in the flowering plant species *Magnolia spp.* Studies on human breast cancer cell lines MCF7 and MDA-MB-231 in cell culture revealed elevated activation of AMPK through the LKB1 pathway. The LKB1-AMPK pathway's capacity to stop breast cancer carcinogenesis was demonstrated by the reduced ability of the breast cancer cells to move and invade. Additionally, honokiol and rapamycin in combination therapy had a synergistic effect on inducing apoptosis in breast cancer cells. As a result, honokiol's potential as a breast cancer treatment is further enhanced by its ability to target the mTOR pathway.

HER2-POSITIVE TARGETED THERAPIES

Tyrosine kinase inhibitors

A significant subtype of breast cancer, accounting for 20%-25% of cases, is breast cancer that is HER2-positive. Due to the prevalence of HER2-positive breast cancer cases, the HER2 receptor pathway is a major focus for cutting-edge and developing targeted breast cancer therapies. According to Mitri Z, et al. (2012) [60], the human epidermal growth factor receptor 2 belongs to the EGFR/ERB family of tyrosine kinase receptors and is a transmembrane protein receptor. Breast cancer and other malignancies, such as gastric and ovarian cancers, depend on HER2 overexpression for cellular change and carcinogenesis. Monoclonal antibodies and tyrosine kinase inhibitors are the two primary targeted treatments for the HER2 pathway that have been demonstrated to be successful (TKIs). Tyrosine kinase inhibitors are microscopic substances that bind and block the HER2 receptor's ATP-binding regions to stop phosphorylation, whereas monoclonal antibodies like trastuzumab primarily target HER2 receptor-binding areas, preventing downstream signalling. TKIs have recently gained

popularity because of their many benefits of oral deliveries, reduced cardiotoxicity, and the ability to target a variety of targets over monoclonal antibody treatments.

Lapatinib, the first TKI to get FDA clearance, was authorised in 2007 for use in patients with HER2-positive, ER-negative, and PR-negative breast cancer who had previously received anthracycline-type therapies, taxane, and trastuzumab. Lapatinib is a dual HER2 and HER1 receptor inhibitor that binds to their intracellular ATP-binding regions competitively and irreversibly to suppress the growth of tumours. For HER2 overexpressing hormone receptor-negative breast cancer patients, lapatinib has little effect on the HER1 receptor. In 2010, letrozole and lapatinib were approved as the first-line treatments for metastatic breast cancer with postmenopausal hormone and HER2 receptor co-expression. In 2013, lapatinib's approval was expanded to allow for usage both during and after chemotherapy treatment and without chemotherapy when combined with trastuzumab. Trastuzumab's ability to induce apoptosis was discovered to be enhanced when coupled with lapatinib. Grade 3-4 diarrhoea and potential liver and heart toxicity were identified to be the most serious side effects of lapatinib. The main techniques used to identify both acquired and innate resistance to lapatinib were mutations in the HER2 tyrosine kinase domain, activation of compensatory mechanisms, and overexpression or amplification of the gene-producing trafficking protein particle complex. Neratinib was more recently authorised by the FDA in 2017 for use as adjuvant therapy for breast cancer with early-stage HER2 overexpression. Neratinib is an irreversible TKI for HER1, HER2, and human epidermal growth factor receptor 4, whereas lapatinib is a reversible TKI for HER2 and HER1 (HER4). The way neratinib works also differs just a little. The HER1, HER2, and HER4 receptors' ATP-binding domain need to be protected against phosphorylation, it causes the covalent bonding of cysteine residues (Cys773 and Cys-805) instead of competitive inhibition. Grade 1-3 diarrhoea and potential hepatotoxicity were shown to be neratinib's most severe side effects, similar to lapatinib. Neratinib resistance is still poorly understood, but associations with increased cytochrome P450 3A4 metabolic activity have been made. In 2018, Pyrotinib, an irreversible TKI of HER1, HER2, and HER4, received preliminary approval in China for the treatment of advanced metastatic HER2-positive breast cancer patients who had previously had capecitabine and conventional anthracycline or taxane chemotherapy. Pyrotinib inhibits phosphorylation and the activation of downstream pathways by forming a covalent bond with the ATP-binding regions of intracellular receptors. Studies for resistance mechanisms as well as clinical trials to assess pyrotinib's safety and effectiveness are still ongoing. The FDA most recently approved tucatinib in 2020 to treat metastatic breast cancer that is HER2-positive. When compared to other TKIs, tucatinib is incredibly selective; it has been demonstrated to be 1000 times more specific to HER2 than EGFR.

Tucatinib is now in the lead for prospective therapy of HER2-positive metastatic breast cancer with CNS metastases since it has been demonstrated to have better Central Nervous System (CNS) penetration than either lapatinib or neratinib. TKIs continue to be a type of targeted HER2-positive breast cancer treatment that is thoroughly studied. The treatment of HER2-positive breast cancer that has progressed to the central nervous system is made possible by TKIs' capacity to cross the blood-brain barrier, and the expanding use of TKIs in the management of metastatic breast cancer presents a bright future for TKI research.

Monoclonal antibodies

Monoclonal antibodies are a successful treatment option for HER2-positive breast cancer, as was described in the part above. Although monoclonal antibody treatments have been around for more than 20 years, trastuzumab only obtained FDA approval in 1998. Trastuzumab is a first-line treatment option for metastatic HER2-positive breast cancer when paired with chemotherapy. By attaching to the HER2 receptor, trastuzumab inhibits downstream signalling that promotes cell proliferation through a variety of methods. The HER2 receptor homodimerization, HER2 receptor extracellular domain cleavage, and HER2/HER3 heterodimerization inhibition are a few of these mechanisms. The HER2 signalling cascade is activated through dimerization and cleavage, respectively. Additionally, by triggering the immune system's antibody-dependent cell-mediated cytotoxicity, trastuzumab aids in the elimination of HER2-positive cells (ADCC). Other immunotherapies for cancer that we will address in a later section also include the immune system being activated to attack cancer cells, so it is not just HER2-targeted monoclonal antibodies that do this. Trastuzumab resistance mechanisms have recently been addressed by modifications to monoclonal antibody regimens for HER2-positive breast cancer that may also improve trastuzumab's effectiveness. Pertuzumab, a monoclonal antibody that binds to the opposite side of the HER2 receptor from trastuzumab, received FDA approval for usage in late 2017. Pertuzumab and trastuzumab used in combination therapy were discovered to work together to inhibit the HER2 receptor more completely. When administered in combination, pertuzumab and trastuzumab reduced cell survival by 60% at a level where neither drug would have any effect alone. The creation of pertuzumab made it possible to address the heterodimerization mechanism of trastuzumab resistance. Margetuximab was developed to boost immune activation against HER2 positive cells and FDA-approved for use with chemotherapy in late 2020. Margetuximab is selective to the same region of the HER2 receptor as trastuzumab and results in the same signalling blockade, despite the fact that the antibody itself is Fc-engineered to have higher affinities for the activating Fc receptor and lower affinities for the inhibitory Fc receptor. It is believed that by intensifying innate and adaptive immune activity against the targeted cell, this engineering will reduce cell survival. The effectiveness of monoclonal antibody therapy for HER2-positive breast cancer is still being studied. The domain of the HER2 single-chain variable section is particularly noteworthy because it can be altered to have dual specificity with a second target protein, potentially improving the anticancer effectiveness of monoclonal antibodies.

Antibody-drug conjugates

Antibody-Drug Conjugates (ADCs) combine the use of antibodies with conventional chemotherapeutic drugs. TheHER2 receptor is targeted with trastuzumab, which inhibits signalling and triggers ADCC to reduce cell survival and proliferation. The antibody-drug conjugates for HER2-positive breast cancer now on the market combine trastuzumab with a chemotherapeutic medication to combine the effects of both systems. There are now two antibody-drug conjugates for HER2-positive breast

cancer that have received FDA approval. Trastuzumab emtansine (T-DM1) was the first ADC to be approved for HER2-positive breast cancer. The microtubule inhibitor mertansine and the trastuzumab backbone that make up T-DM1 are joined via a thioether linker. Recent approval of the second-line drug trastuzumab emtansine for high-risk patients with early-stage residual illness after neoadjuvant therapy. It is used to treat advanced metastatic HER2-positive breast cancer. The ADC was found to be more successful than standard therapy in patients who had undergone extensive pre-treatment, and it seemed to be active in HER2-positive patients with HER2 mutations and variable HER2 expression. Trastuzumab deruxtecan is the second ADC to be authorised for the treatment of HER2-positive breast cancer (T-DXd). In contrast to T-DM1, T-DXd uses an exatecan with a greater drug to antibody ratio, a cleavable linker, and a trastuzumab backbone coupled to a chemotherapeutic agent. Exatecan is a topoisomerase inhibitor as opposed to mertansine, which is a microtubule inhibitor. T-DXd also has an enzymatically cleavable peptide linker, which T-DM1 does not, which may allow the ADC to be more active even in cells with low HER2-expression. Trastuzumab deruxtecan was approved by the FDA for the treatment of patients with HER2-positive breast cancer who had received at least two prior HER2-targeting treatments. Low-grade adverse reactions to both ADCs include nausea and gastrointestinal damage. To develop into the next-generation of ADC technology for the treatment of HER2-positive breast cancer, numerous HER2-specific ADCs are presently undergoing clinical trials. New linking technologies and a variety of different payloads are used in the new ADCs. The integration of the duocarmycin payload in the pro-drug seco-suocarmycin version of trastuzumab duocarmazine makes it unique. Others stand out for utilising antibodies with distinct epitopes, including XMT-1522.

HER2-NEGATIVE TARGETED THERAPIES

Parp inhibitors

The nucleus is home to a group of enzymes called poly-ADP ribose polymerase (PARP), which is strongly associated to DDR. According to Brown JS and colleagues (2017), it primarily plays a role in gene transcription, cell differentiation, and death. Inhibiting PARP function in breast cancer cells can prevent the DNA from being repaired normally, cause DNA damage to accumulate, and cause replication fork folding that results in double-strand breaks, which kills the breast cancer cells. Numerous caspases have the ability to break PARP, which is thought to be a key sign of cell death. As a result, the therapeutic potential of PARP inhibitors (PARPi) for the treatment of breast cancer is satisfactory. For instance, the currently available drugs olaparib, niraparib, fluazolepali, and pamiparib have demonstrated good efficacy. According to pertinent studies, BCRA1/2 mutant cells can become more sensitive to PARP inhibitors. Women who carry the tumour suppressor gene BRCA1/2 run an 85% lifetime chance of developing breast cancer. Accordingly, early research focuses on breast cancer patients with BCRA1/2 mutations who are treated with PARP inhibitors. The first PARP inhibitor approved for the treatment of breast cancer with a BRCA mutation is olaparib. Olaparib has lower side effects and higher safety compared to other treatments for BRCA-mutated and HER2-negative breast cancer patients, according to pertinent data from clinical trials. PARPi affects DNA damage repair, which has an anti-tumour impact. It can compete for binding with PARP enzyme and trap PARP at the site of DNA damage in addition to inhibiting PARP enzyme's catalytic activity. As a result, it causes PARP1/2 to remain in the vicinity of the DNA break, which can inhibit DNA repair and aid in the transformation of single-strand breaks into double-strand breaks. The loss of enzymatic activity may not even be as harmful to cells as this PARP trapping effect. In any case, it is now well acknowledged that a sort of iron-dependent programmed necrosis called iron apoptosis is a major component influencing the development and spread of many malignancies. According to recent research, ferroptosis helps PARP inhibitors partially achieve their therapeutic goal. In a p53-dependent way, PARPi inhibits the expression of the cystine transporter SLC7A11, which reduces glutathione synthesis, encourages lipid peroxidation, and results in ferroptosis. As a result, individuals with breast cancer may benefit more from treatment when Ferroptosis Inducers (FINs) and PARP inhibitors are used together.

CDK inhibitors

When cyclin and Cyclin Dependent Kinase (CDK), a crucial kinase involved in controlling the cell cycle, unite, they create an active heterodimer that is crucial for both the start of the cell cycle and the control of transformation at every stage. There are currently around 20 different types of CDKs known. Among these, CDK1, CDK2, CDK4, and CDK6 are involved in controlling the cell cycle. Breast cancer occurs and develops when cyclin is overexpressed or overactivated, CDKI activity is inhibited, and the ongoing activation of upstream fission signalling results in the deregulation of CDK activity. These events either directly or indirectly result in unchecked cell proliferation and genome instability. Since CDK activity is required for the development of breast cancer cells, CDK has long been regarded as a promising target for the development of effective treatments. Numerous CDK inhibitors are currently being studied in either preclinical or clinical settings. These inhibitors can be categorised into ATP competitive and non-competitive inhibitors based on their various modes of action. When ATP-competitive CDK inhibitors bind to CDK protein, they imitate the ATP structure and have an inhibitory impact, and these CDK inhibitors' development is moving along rather well. Due to the first-generation inhibitors' lack of selectivity for various types of CDK and severe adverse effects in human trials, such as flavopiridol, roscovitine, UNC-01, etc., their development was halted. The second generation of CDK inhibitors, on the other hand, exhibit better anti-tumour activity and selectivity, particularly those that target CDK4/6 like palbociclib, ribociclib, abemaciclib, etc., which can inhibit RB phosphorylation and block the cell cycle in G1 phase, preventing the spread of breast cancer. When used in conjunction with endocrine therapy, clinical trials have demonstrated that it has good efficacy in the treatment of HR+ and HER2-positive metastatic breast cancer. Because ERa-positive breast cancer frequently overexpresses cyclin D, CDK4/6 inhibitors are being utilised widely in the treatment of breast cancer, but only in individuals with this kind of cancer. RB1 mutations and/or deletion are common in HER2-negative breast tumours, which restricts the use of CDK4/6 inhibitors. Certainly, the expression of the Androgen Receptor (AR) is positively correlated with RB, which encourages the activation of cyclin D, indicating that CDK4/6 inhibitors have a lot of promise for the treatment of HER2-negative breast cancer that expresses the Androgen

Receptor (AR) positively. Related trials that paired the CDK4/6 inhibitor abemaciclib with the androgen biosynthesis and AR activity-targeting drug seviteronel showed synergistic benefits in TNBC animals with AR positivity. To treat AR-positive TNBC, cell cycle inhibitors can be utilised in addition to medications that target the AR. Non-ATP-competitive CDK inhibitors have taken a while to develop. Peptides and artificial small compounds that resemble naturally occurring CDK inhibitors like p21, p27, and p25 are the main types of such inhibitors. It has become possible to interfere with CDK and the cyclin complex using a variety of innovative techniques, including inhibiting substrate recognition, concentrating on crucial protein-protein interactions, aiming for conformational change-related residues, etc., and as a result, heterogeneous inhibitors and inhibitors against substrate competition are produced. Inhibitors of substrate competition primarily stop CDK and cyclin from binding, reducing CDK activity. Currently, these inhibitors are being improved upon to create better CDK2 polypeptide analogues that act as drug-like inhibitors. According to the study, the heterogeneous inhibitor often binds close to the ATP binding site, interfering with the enzyme's conformational change and having good selectivity. ABL/P38 and MEK1 inhibitor research and development have had success with heterogeneous inhibitors. It is a strategy with considerable potential for the development of CDK inhibitors and the treatment of breast cancer.

Antibody-drug conjugates

Antibody-drug conjugates, which are used to treat HER2-positive breast cancer, are composed of a monoclonal antibody and a strong chemotherapeutic medication, as was discussed in the ADC section above. In contrast to ADCs that are used to treat HER2-positive breast cancer, sacituzumab govitecan (IMMU-132) targets triple-negative breast cancer cells utilising an anti-human trophoblast cell-surface antigen 2 (Trop-2) monoclonal antibody. Anti-Trop-2 antibody IMMU-132 is linked to topoisomerase I inhibitor SN-38 via a cleavable CL2A linker. Breast cancer cells contain the protein Trop-2. Because of this, IMMU-132 can deliver SN-38 via the cleavable linker to the breast cancer cells and the surrounding tumour with specificity thanks to the anti-trop-2 antibody. The medicine sacituzumab govitecan was approved by the FDA in 2020 for the treatment of metastatic triple-negative breast cancer in patients who had had at least two prior metastatic therapy.

IMMUNOTHERAPY

Immune checkpoint inhibitors

The immune system's function in the therapy of breast cancer is currently being carefully investigated. It has been demonstrated that activating tumour-infiltrating lymphocytes can improve the prognosis of breast cancer. Immune checkpoint inhibitors were created primarily to boost the immune response by activating cytotoxic T cells against aggressive malignancies. Immune checkpoint drugs for breast cancer specifically target the PD-1/PD-L1 axis (programmed cell death protein 1/programmed cell death ligand 1) due to its specific influence on the disease the cytotoxic T lymphocyte-associated antigen 4 checkpoint, and other immunological checkpoints. As a control mechanism, the PD-1/PD-L1 relationship prevents the activation of cytotoxic T cells. When the PD-1/PD-L1 axis is disrupted, cytotoxic T lymphocytes become more activated, making it easier for them to infiltrate and attack the breast cancer tum-
-our.

Numerous monoclonal antibodies have been developed particularly to target and block the PD-1/PDL1 axis. Two of these antibodies in particular have been reported to be effective when used with chemotherapy for advanced triple-negative breast cancer. Especially, pembrolizumab (PD-1-binding) and atezolizumab (PD-L1-binding) had only a minor effect when taken alone against severely pretreated TNBC patients; however, both antibodies showed a considerable increase in efficacy when combined with chemotherapy. Pembrolizumab and atezolizumab have both been authorised for treatment in individuals with advanced-stage TNBC. Two more monoclonal antibodies that focus on the PD-1/PD-L1 interaction are durvalumab and nivolumab. Although these antibodies have demonstrated potential in the fight against other malignancies such as small-cell lung cancer, they have not been licenced for use against breast cancer. Although chemotherapy and durvalumab have shown potential in treating early-stage TNBC, this application has not yet been authorised. A novel treatment option for breast cancer, immune checkpoint inhibitors is still being researched and developed.

Cancer vaccines

The therapeutic potential of cancer vaccines is a growing topic of research in the field of breast cancer treatment. Aiming to assess the effectiveness of cancer vaccines in the treatment of cancer and the prevention of cancer recurrence, current research and clinical trials are being conducted. To increase the production of long-term memory cluster of differentiation 8 positive (cytotoxic) T cells and cytotoxic T-lymphocytes that target the tumour and prevent a recurrence, cancer vaccines function by stimulating the patient's immune system. Additionally, vaccinations typically have lower toxicity as compared to chemotherapy and do not need to be administered as frequently as conventional cancer therapies. Peptide vaccines are the main topic of interest for breast cancer vaccines in cancer vaccine research. Introducing specific tumour antigens that are not present in healthy tissue, Prompting the immune system to recognise and target these antigens in cancer cells is the goal of peptide vaccines. Numerous ongoing clinical trials are investigating the efficacy and security of cancer vaccines in adjuvant and neoadjuvant settings, particularly for HER2-positive and aggressive triple-negative breast tumours. An in-depth study is being done on the E75 peptide vaccine, also known as nelipepimut-S, which prevents breast cancer. By adding a nine amino acid peptide that is "derived from the extracellular region of the HER2 protein," E75 targets breast tumours that are HER2-positive. By binding to the major histocompatibility complex class 1 glycoproteins of the human leukocyte antigen-A2 (HLA-A2) serotype, E75 is predicted to stimulate the cytotoxic T-lymphocyte response. In phase 3 clinical research, the ability of E75 to prevent breast cancer recurrence when combined with the immunoadjuvant Granulocyte-Macrophage Colony-Stimulating Factor (GMCSF) was examined (PRESENT). However, co-treatment with E75 and GM-CSF failed to show any therapeutic advantage in preventing cancer recurrence. The efficacy of GP2, a different breast cancer vaccine, in reducing the recurrence rate in patients with HER2-positive breast cancer has also been studied. GP2 is derived from a nine-amino acid peptide from the transmembrane domain of the HER-

-2 protein. GP2 is projected to bind to HLA-A2 and activate cytotoxic T cells, albeit with lower affinities than E75. Despite showing clinical safety, the vaccination did not show any appreciable therapeutic benefit. To find cancer vaccines that work as both preventative and therapeutic measures, additional peptide vaccines that target various tumour antigens are being researched as both monotherapies and as combination therapies. The FDA authorised the investigation of a preventive TNBC vaccine created by Dr Vincent Tuohy of the Cleveland Clinic in December 2020. Phase 1 clinical trials with Anixa Biosciences will assess the effectiveness of this vaccination in postmenopausal patients with high-risk, early-stage TNBC. Alpha-lactalbumin, a protein that is only expressed in the mammary glands during lactation, is a protein that is specifically introduced by this vaccine. It was discovered that TNBC, in particular, had abnormally high amounts of alpha-lactalbumin expression. Therefore, postmenopausal women may benefit greatly from this vaccine's preventive and therapeutic potential. In addition to peptide vaccines, clinical trials are still being carried out to assess the efficacy of full protein vaccines, bacterial/viral vaccines, cell-based vaccines, and gene-based vaccines in the treatment of breast cancer. Due to their capacity to bind both HLA class I and II epitopes and circumvent particular HLA constraints, whole protein vaccines may be preferable to peptide ones. Antigen-Presenting Cells (APCs) can be infected with viral vaccines to cause the production of transgenes that are specifically found in tumour cells. Additionally, the therapeutic potential of some oncolytic viruses can be increased by utilising them against tumour cells. Cell-based immunizations introduce autologous tumour-cell-based vaccines or allogeneic tumour-cell-based vaccines to elicit an immune response against many Tumour-Associated Antigens (TAAs). Gene-based immunizations, such as DNA vaccines, and transfect APCs, cause the transfected APCs to express TAAs. This method enables APCs to produce a potent immune response against TAAs present in the DNA vaccine.

CONCLUSIONS

There has been a significant advancement in the search for treatments for all subtypes of breast cancer recently, involving a variety of techniques ranging from signalling blockades to the induction of the immune system through vaccination. Treatment options for breast cancer have significantly grown thanks to the development of targeted and immunological treatments, particularly for late-stage, metastatic breast tumours. There is still a lot to look forward to for breast cancer treatment in the future, as seen by the recent approval of multiple new breast cancer medications. The targeted medicines we looked at have changed the way breast cancer is treated and given hope to people who are still awaiting a diagnosis.

DECLARATION OF INTEREST

The authors declare no conflicts of interest.

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