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Review Article

ADVANCES AND NOVEL THERAPIES FOR THE TREATMENT OF DIFFERENT SUBTYPES OF BREAST CANCER

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ABSTRACT
The treatment regimen for breast cancer depends upon the sub-type of breast cancer which is basically divided into three types; luminal A, luminal B and Triple-negative breast cancer. Chemotherapy and surgery being the conventional therapy for treating all types of cancer although effective, has limitations leading to the drug resistance and recurrence of the disease, therefore studies are conducted to discover the specific targets to kill the cancer cells without harming other cells and with much effort drugs are developed against targets such as estrogen receptors, progesterone receptors, and HER2 receptors to treat the luminal A and Luminal B subtype of breast cancer, use of Tyrosine Kinase Inhibitors has also been validated, the effectiveness of CDK4/6 inhibitors in treating the luminal A breast cancer has been conducted with significant results. Among the different subtypes of cancer, TNBCs are the most difficult to treat due to lack of HR receptors and HER2 receptors, they are the most invasive types of breast cancer and leave only chemotherapy and surgery as the treatment but, recent studies have tried to evaluate the effectiveness of PARP inhibitors, EGFR inhibitors to treat cancer with a good result. In this review paper, an effort has been made to document different novel therapies for the treatment of the three subtypes of breast cancer with the clinical trial data to assess the effectiveness of different drugs in combination with other drugs and to find out the possible way for drug resistance and recurrence of cancer.

Keywords: Luminal A, Luminal B, Triple-negative breast cancer, PARP inhibitors, Endocrine therapy, mTOR inhibitors.

1. INTRODUCTION
Cancer is a cellular disease in which the cells lose their control over their growth and grow and divide indefinitely and due to its property of metastasis, spread to the different parts of the body. Human body is composed of trillions of cells and cancer being cellular disease is not restricted to particular organ or tissue and can generate in any part of the body. Cells grow and divide through a process called cell division, as old cells worn out and die, new cells take their place, but due to various reasons this process fails and the cells keeps on growing uncontrollably without dying, these cells forms tumor, which can be cancerous or non- cancerous. The total number of deaths estimated for cancer in 2020 was 10 million, with 2.6 million new cases of breast cancer alone claiming the life of 685000 individuals worldwide. This makes breast cancer the deadliest form of cancer in women [1-5].

As most of the cancer results from the mutation in the DNA, the genes that are associated in the development of breast cancer is categorized under three types:

1) High penetrance, low frequency genes (*BRCA1* & *BRCA2)*: Mutation in these two genes account for more than half of the inherited breast cancer, it confers the risk of 10 to 30 times as compared to the women who does not have mutation in these genes.
2) Moderate penetrance, low frequency: Till date four genes have been identified which poses the elevated but moderate risk of developing breast cancer and

they are *CHEK2, ATM, BRIP1*, and *PALB2.* These genes exert 2-3 times higher risk in the mutation carrier than in normal.

3) Low penetrance, high frequency: Total of 10 genes have been found by now which despite having high frequency have been related to low risk of developing breast cancer in women when present alone on the order of less than 1.5.

2. TYPES OF BREAST CANCER

Breast cancer has generally divided into four molecular subtypes depending upon the hormone receptors and other proteins related to the breast cancer, the risk factor of the incidence, the treatment, diagnosis, prognosis will all depend upon the subtype of cancer developed. The four types are:

2.1. Luminal A or HR+/HER2-(HR- positive/ HER2- negative)

Most of the women getting affected by the breast cancer is of Luminal A type. These subtypes tend to grow at slower rate as compared to other subtypes. They are known as HR-positive because of the hormone receptor they are associated with, they are ER (estrogen receptor) positive and/or PR (progesterone receptor) positive. They are also known as HER2-negative i.e., Human epidermal growth factor receptor 2, HER2 plays an important role in cell growth and repair in healthy breast cancer cells [6-10].

2.2. Luminal B or HR+/HER2+ (HR- positive/ HER2- positive)

They grow faster than the luminal A subtypes and are more aggressive. They are positive for both Hormone receptor and HER2 leading to production of higher-than-normal amount of HER2 protein.

2.3. Triple negative or HR-/HER2- (HR/HER2- negative)

In this type of cancer, the cells do not have receptors for estrogen, progesterone and Human epidermal growth factor receptor, they are usually invasive and starts at the ducts. Women with breast cancer of the type HR+/HER2- can be treated using hormonal therapy and breast cancer with high amount of HER2 receptor can be treated by anti-HER2 targeted therapy using drugs such as trastuzumab, but in women with triple negative subtype cannot be treated using anti-HER2 or hormone therapy and can be treated by chemotherapy, radiotherapy.

2.4. HER2-positive

In US, 1 out of 5 women suffering from breast cancer is of this subtype, they are ER- and PR- negative and HER2-positive with the enhanced production of the HER2 receptor protein on the cell surface due to which there is excessive growth because cell absorb too much of a substance known as epidermal growth factor 2 which promotes cell growth. The symptoms of HER2-positive breast cancer are similar to the other breast cancer types which include lump in breast, pain, change in breast shape, abnormal discharge and swelling. Depending upon the stage, HER2 positive breast cancer can be treated by surgery, radiotherapy, chemotherapy, immunotherapy, and a combination of these [11-13].

3. SEARCH METHODOLOGY

In this study, we have studied 36 papers on breast cancer and its subtypes, and 8 papers were excluded because these did not meet the study objectives. The selected papers were from valid sources such as PubMed Central, Scopus, Medline, EMBASE, Google Scholar, from 2011 to 2021 in the English language.

3.1. Inclusion criteria

Premenopausal women, postmenopausal women, treatment for breast cancer and Paper from 2011-2021.

3.2. Exclusion criteria

Breast cancer in men, prevention of breast cancer and papers published before 2011.

4. TREATMENT AND THERAPY PLAN FOR LUMINAL A BREAST CANCER

As discussed already that luminal A breast cancer include HR+ (ER+ &/or PR+) cancer cells, these cancers can be treated using endocrine therapy which blocks the hormone receptors or lowers the level of hormone.

4.1. Drugs that block estrogen receptors

Tamoxifen- These drugs blocks estrogen from binding to its receptor and signalling cells to grow and divide. While tamoxifen acts as anti-estrogen in some tissue like uterus and bones. It acts as estrogen that is why they are known as selective estrogen receptor modulator (SERM)

Fulvestrant- They function by blocking and damaging the estrogen receptor, unlike SERM, they act as anti-estrogen throughout the body.

4.2. Drugs that lower estrogen level

Aromatase inhibitor- In the post-menopausal women, estrogen is produced by fatty tissue using the enzyme aromatase. Aromatase inhibitor stops the functioning of aromatase thus lowering the estrogen production. Example include Anastrozole, Letrozole etc.

Till date there are several endocrine therapies developed, some of them are selective estrogen receptor down regulators (SERD), selective estrogen receptor modulator (SERM), luteinizing releasing hormone agonist (LHRH) and aromatase inhibitor (AI).

4.3. Effect of neo-adjuvant endocrine therapy on early breast cancer

The main motive behind the neoadjuvant therapy in the case of breast cancer is mostly similar to the other clinical subtypes:

- To reduce the size of the tumor such as to facilitate the breast-conserving therapy (BCT)
- To improve the progression-free survival (PFS) and overall survival (OS)

One of the randomized clinical trial named cancer and leukemia group B (CALGB 9343) were conducted with the objective to understand the efficacy of tamoxifen alone or along with radiation therapy to treat ER-positive breast cancer. The study reported that at the median follow up period of 12.6 years, 90% patients who received tamoxifen alone compared to the 95% patients who received tamoxifen along with radiation therapy, were free from the recurrence of breast cancer [1].

In one of the other trials named Adjuvant Tamoxifen Longer Against Shorter Trial (ATLAS), the two durations of administering Tamoxifen was compared and it reported that women who were ER-positive when given the treatment of tamoxifen for 10 year as compared to stopping at year 5 has lower recurrence of disease (617 recurrence among 3428 patients given tamoxifen vs 711 recurrences among 3418 controls), they also showed reduction in mortality rate (Tamoxifen= 639 deaths vs Control= 722 deaths) [2].

For the longest time, tamoxifen has been used to treat the HR-positive breast cancer as it has shown that treatment for 5 years reduces the risk of death by 26% and lowers the risk of recurrence by 47%. but it being SERM, causes increase in the estrogen levels in endometrium causing endometrial hyperplasia, hot flushes and vaginal disorder has been reported [3].

Another class of drug that is used as an endocrine therapy is Aromatase inhibitors that include anastrozole, letrozole and exemestane. In post-menopausal women, the ovaries stop the production of estrogen, so the only source of estrogen production in the women is fatty tissues which with the help of enzyme aromatase thus using aromatase inhibitors can reduce the risk of developing cancer in post-menopausal women.

It has long since been a topic of debate as to which treatment is better in case of HR-positive cancer, is it the upfront treatment (where aromatase inhibitor is given to the patient) or switch treatment (where aromatase inhibitor is given after 2 years of treatment with tamoxifen) and also which among anastrozole, letrozole and exemestane has better outcome in the patients.

This issue has been tried to resolve in the trial named FATA-GIM3 which is a randomized phase 3 trial and was reported that at 5 years, 88.5% and 89.8% was the disease-free survival for switch treatment and upfront regimen respectively and overall survival for 5 years with switch schedule was 95.3% whereas with upfront treatment it was 96.8% [3].

In the comparison among different aromatase inhibitors, it was found that for anastrozole, letrozole and exemestane the disease-free survival at 5 year was 90%, 89.4% and 88% respectively [5].

4.4. Cyclin dependent kinase 4 & 6 (CDK 4/6) inhibitors

As stated earlier, endocrine/hormonal therapy is the mostly used treatment regimen in the case of HR-positive breast cancer but it too has its shortcoming as one-third of the cases relapse [4]. The main factor driving the breast cancer cells to become tolerant to the hormonal therapy is still not known but some studies have shown that obesity is linked to the relapse and it demonstrated the capability of the secretome collected from the adipocytes of the obese person to reduce the anti-proliferative effect of tamoxifen [5].

One of the proteins that is responsible in deciding whether the cell should divide or enter into quiescent state is a negative regulator of cell cycle progression i.e., retinoblastoma (RB) associated protein which acts by repressing the E2F family of transcription factor, the activity of this protein is disrupted upon hyper-phosphorylation carried out by the complex constituting cyclin D, CDK 4 or CDK 6. In breast cancer, there is an amplification of the Cyclin D, CDK4 & CDK 6 with 29% patients having amplified Cyclin D and 14% patient with CDK 4 [6].

The three most common drugs under this category are

Palbociclib, Ribociclib and Abemaciclib.

In one of the double-blind, phase 3, randomized study conducted to compare the efficacy of fulvestrant given alone, with the palbociclib, the trial reported that patient given palbociclib along with fulvestrant has a better progression free survival (9.2 months) than the patient given fulvestrant (3.8 months when given with placebo) [7].

Open label, randomized phase 2 study named PALOMA-1/TRIO-18 was conducted to assess the safety and efficacy of palbociclib given along with letrozole compared to the letrozole given alone is the case of estrogen receptor positive breast cancer. The analysis of the final data revealed that the median progression free survival was 20.2 months in the case of letrozole plus palbociclib group vs mere 10.2 months for letrozole only group. Although, the number of adverse events noted which led to the dose interruption was higher in case of letrozole plus palbociclib group (33%) as compared to only 4% in case of letrozole alone group [8].

Post-menopausal patients with estrogen-positive, HER2-negative advanced breast cancer showed that ribociclib plus letrozole has a better progression free survival than letrozole alone in the clinical trial named MONALEESA-2 [9].

The safety and efficacy of ribociclib plus letrozole as compared to the letrozole alone in case of pre-menopausal HR-positive, HER-2 negative breast cancer women were studied in the phase 3 trial MONALEESA-7. The progression free survival noted for the ribociclib group was 23.8 months as compared to 13 months for the placebo group. Patients who received tamoxifen along with the ribociclib showed the median progression free survival of 22.1 months versus 11 months for the placebo group. Patients who received Non-Steroidal Aromatase Inhibitor in combination with ribociclib demonstrated the Progression free survival of 27.5 months as compared to 13.8 months when given in combination with placebo group [10].

The double blind, randomized, phase 3 trial named MONARCH 3 was conducted to study the effect of abemaciclib or placebo plus the non-steroidal AI such as anastrozole or letrozole in a luminal A subtype breast cancer. In the median follow-up period of 17.8 months, the PFS did not reach in the case of abemaciclib group and was 14.7 months in the placebo group. The objective response rate in the group received placebo was 34.5% as compared to 48.2 % in the abemaciclib group. Thus, abemaciclib along with the AIs is better than the AI alone as a first-line treatment of HR+/HER2- breast cancer with a tolerable safety profile in post-menopausal women [11].

4.5. Phosphatidylinositol 3-kinase (PI3K)/ Protein kinase B (AKT)/ Mammalian target of Rapamycin (mTOR) pathway inhibitors

Cell physiology such as motility, proliferation, growth, survival is governed by various cellular pathways and PI3K/AKT/mTOR pathway is one such crucial pathway which regulates the physiology by inducing signal transduction in response to the extracellular stimuli. It is found that in various types of cancer there is a mutation in these pathways and 60% of breast cancer harbors mutations of such sort which overexpresses the PI3K/AKT/mTOR pathway [12].

One of the major roadblocks in using endocrine therapy is the development of resistance in cancer cells against drugs such as tamoxifen leading to the recurrence of disease. Some studies have tried to understand the factors responsible for it and observed that tumor-associated macrophages are responsible for the induction of tamoxifen-resistance in breast cancer cells [13]. In subsequent studies, the mechanism underlying the TAM associated resistance was covered and was found that TAM induces the secretion of CCL2 which in turn activates the PI3K/AKT/mTOR pathway [14].

Therefore, drugs that can target and inhibit the PI3K/AKT/mTOR pathway can help treat cancer as well as prevent cells from becoming resistant to endocrine therapy.

4.6. PI3K Pathway inhibitors

The most commonly used PI3K inhibitor is alpelisib. SOLAR-1 trial was conducted to evaluate the efficacy of alpelisib plus fulvestrant given to patient as compared to placebo plus fulvestrant in the group of patients who previously received the endocrine therapy against HR-positive/HER2-negative breast cancer and the two groups were created on the basis of PIK3CA mutation status. The analysis of the data showed that the patient group with PIK3CA mutation has a progression free survival of 20 months in alpelisib-fulvestrant arm and 5.7 months in the placebo-fulvestrant arm. Overall response in the case of alpelisib-fulvestrant arm was 26.6% as compared to 12.8% in case of placebo-fulvestrant arm. Although, the adverse event was noted such as hyperglycemia (Placebo-fulvestrant group accounted for 0.7% and alpelisib-fulvestrant group accounted for 36.6%), 9.9% patients who received

alpelisib-fulvestrant arm suffered from rashes as compared to 0.7% who received placebo-fulvestrant [15].

4.7. mTOR pathway inhibitors

One of the most prescribed drug as mTOR pathway inhibitor to treat HR+/HER2- breast cancer is everolimus and it also has received FDA approval to treat breast cancer in combination with exemestane after the failure of aromatase inhibitors.

To understand and evaluate the efficacy of everolimus, the trial named BOLERO-2 was conducted and the comparison was done between the group of patients who received everolimus plus exemestane and exemestane plus placebo. The results showed that the median progression-free survival for everolimus and exemestane group was 6.9 months as compared to the 2.8 months for placebo plus exemestane group. Adverse events were found to be more associated with the everolimus plus exemestane arm than the other group, accounting for 8% of patients who received everolimus plus exemestane with stomatitis vs 1% patient who were given placebo plus exemestane, hyperglycemia cases were seen in 4% patients who received everolimus plus exemestane compared to less than 1% who received alternative regimen [16].

In yet another trial, the efficacy of everolimus was compared with the fulvestrant in case of the HR+/HER2- breast cancer. In this trial, the effectiveness of fulvestrant when given alone was compared to fulvestrant given in combination with everolimus. The data obtained from the study highlighted that median progression-free survival was 5.1 months in the group who received fulvestrant alone and that it was increased to 10.3 months in the group in which everolimus in combination with fulvestrant was administered. Also, the clinical benefit rate was strikingly higher in case of everolimus group (63.6% as compared to 41.5%). The adverse events were more prominent in the everolimus arm [17].

5. TREATMENT AND THERAPY PLAN FOR HER2-POSITIVE BREAST CANCER

It was estimated that 276,480 cases of breast cancer will occur in the women of US and 15-20% of the cases will be of HER2-positive subtype [18].

Several drugs alone or in combination with other drugs and radiotherapy is used to treat the HER2-positive breast cancer. The classes of drugs for this subtype are anti-HER2 monoclonal antibody such as trastuzumab and pertuzumab (different target site than trastuzumab), Antibody-cytotoxic agent conjugate such as ado-trastuzumab-emtansine has also been used in case of HER2-positive breast cancer. Effectiveness of dual tyrosine kinase inhibitors in treating the breast cancer has also been studied.

5.1. Anti-HER2 monoclonal antibody

Two drugs that are used as anti-HER2 monoclonal antibody are trastuzumab and pertuzumab. Trastuzumab improves the outcome in the patients suffering from HER2+ breast cancer but, most cases of the advanced cancer tend to progress and, in such case, the pertuzumab the other anti-HER2 monoclonal antibody which prevents the receptor dimerization has an activity complementary to the trastuzumab thus the combination therapy has shown to have better outcome than treating with either drug alone [19].

It was noted that the progression-free survival for the control group (placebo plus trastuzumab plus docetaxel) was 12.4 months whereas in the pertuzumab group (pertuzumab plus trastuzumab plus docetaxel), it was 18.5 months and cardiac toxic effect was not increased significantly [19].

5.2. Antibody-cytotoxic agent

Antibody-cytotoxic agent is a complex of an antibody i.e., trastuzumab and a drug that is a cytotoxic agent i.e., emtansine (DM1) which is a microtubule inhibitor. These drugs are found to be effective in treating the patients who have been previously exposed to chemotherapy and HER2 targeted therapy [20].

Studies were conducted to analyze the potential of trastuzumab-emtansine to treat the HER2-positive breast cancer and in one of the trials, it was observed that the percentage of patients who were free of invasive cancer at three years was 88.3% for the group who received trastuzumab-emtansine drug as compared to 77% in the group of patients who received trastuzumab but, a greater number of adverse events was related to the trastuzumab-emtansine than trastuzumab arm [20].

5.3. Tyrosine kinase inhibitors

HER2-positive breast cancer is mostly treated by trastuzumab but, the limitation with trastuzumab is that the cancer cell become resistant to the drug and there is a greater chance of recurrence of the disease and also trastuzumab is associated with cardiotoxicity. TKIs in such cases are though less selective but prevents the cancer cells from becoming resistant by targeting other signaling pathway.

TKIs are small-molecules which compete with the ATP for binding sites in the intracellular catalytic domain of kinase. When TKIs binds to this site, it hinders the protein phosphorylation and thus disturbs the signaling pathway.

Lapatinib is the small-molecule, TKI approved by the FDA to use in the treatment of patients with HER2+ breast cancer, they have reduced adverse effect on cardiac events and capable of crossing BBB (blood-brain-barrier) which is not possible for the monoclonal antibodies, thus, it can used to treat the central nervous system metastases from HER2+ breast cancer [21].

6. TREATMENT AND THERAPY PLAN FOR TRIPLE NEGATIVE BREAST CANCER

TNBCs are one of the subtypes of the breast cancer and so named because of the absence of estrogen receptor, progesterone receptor and HER2 receptor which are present in other two subtypes of breast cancer. This characteristic of the TNBCs make them very difficult to treat due to failure of the targeted therapy. 10-20% of the breast cancers are of this type [22].

Due to the failure of targeted therapy, chemotherapy is the most common and systemic treatment in case of the TNBCs. In regard of the tumor microenvironment, TNBCs are strikingly heterogenous. Good prognosis and response to chemotherapy can be associated with tumor lymphocyte infiltration and this provides strong reason for testing immunotherapies in case of TNBCs [23].

The current novel therapies under study to treat TNBCs are:

6.1. Poly (ADP-ribose) Polymerase (PARP) Inhibitors

Individual having mutation in the *BRCA1* and *BRCA2* are at high risk of developing the breast and ovarian cancer. These two genes have the function as tumor suppressor with the help of protein that is involved in the homologous recombination (HR) repair of double stranded DNA breaks. They mediate their function by recruiting the RAD51 to double stranded DNA breaks which facilitates the HR repair.

In tumors. Base Excision Repair (BER) is crucial for survival and PARP enzymes play an important role in these pathways. PARP is the family of enzymes (PARP1 & PARP2) which are localized to the DNA damage site; these enzymes cause the post translational modification of the nuclear protein by the addition of ADP-ribose. Therefore, when the PARP is inhibited, the DNA repair is stalled. Treatment with PARP inhibitors leads to the accumulation of DNA damage which further results in cell cycle arrest and apoptosis [24].

Olaparib is one such PARP inhibitor which is administered orally and has potential anti-tumor activity in the patients suffering from TNBC.

In one of the randomized phase 3 trial, Olaparib was compared with the standard therapy in a patient who had a BRCA mutation and TNBC. The results of the trial demonstrated that the median progression-free survival was significantly higher in the group who received Olaparib monotherapy (7 months) as compared to the group who were given standard therapy (4.2 months) and also the response rate in the Olaparib group was 59.9% versus the standard therapy group with 28.8% [25].

6.2. EGFR Inhibitors

Although, PARP inhibitors have been effective in treating the TNBCs but the studies has shown that the tumor cells becomes resistant to the PARP inhibitors such as Olaparib. The exact reason for which is not known but it has been observed that the combined use of PARP and EGFR inhibitors have resulted in the effective inhibition of the proliferation of cancer cells and also increases the sensitivity to the treatment with talazoparab in TNBC cells. One of the drugs used as EGFR inhibitor is cetuximab (anti-EGFR monoclonal antibody). The results from clinical trial have shown that the progression-free survival when treated with cetuximab plus cisplatin was 3.7 months as compared to the 1.5 months in the group which only received cisplatin [26-28].

6.3. Immunotherapy

Immune systems distinguish between the self and the foreign agents and launch an immune response eliminating the foreign substances which are injurious to the body. During the development of cancer, cells gain the foreign characteristics but can evade the immune system thus keep on proliferating inside the body thus failing the purpose of immune cells to kill the injurious cells. But in recent studies, it has been shown that blocking monoclonal antibodies that targets cytotoxic T-lymphocytes associated antigen-4 (CTLA-4), programmed death ligand-1 (PDL-1) and programmed death-1 (PD-1) can help regain anti-tumor immunity against various types of cancer.

One of the Immunotherapy drugs on which the studies are carried out is pembrolizumab. In one of the phase 3

trial, patients were divided into two groups where one received pembrolizumab plus paclitaxel and carboplatin whereas the other group was given placebo plus carboplatin and paclitaxel. The result showed that after median follow up period of 15.5 months, disease progression was observed in 7.4% patients who received pembrolizumab and 11.8% patients who received placebo. Thus, clearly justifying the effectiveness of the pembrolizumab as an anti-tumor agent [29].

7. DISCUSSION AND CONCLUSION

Different sub-types of cancer have different characteristics thus different treatment regime has to be followed in order to treat breast cancer. Three sub-types of cancer are luminal A (HR+/HER2-), luminal B (HR+/HER2+) and Triple negative breast cancer (TNBC). In luminal A there is overexpression of estrogen and progesterone receptor and thus endocrine treatment has been found to be useful in treating such type of cancer. The most common used drug is tamoxifen which is considered as SERM, the effectiveness of tamoxifen is well known but the studies has shown that it is rendered harmless to cancer cells due to development of the drug resistance. Another class of drug known as aromatase inhibitor which include anastrozole, letrozole and exemestane has shown anti-tumor activity in treating the ER-positive breast cancer, debate regarding the effectiveness of aromatase inhibitor as compared to the tamoxifen was settled in the trial named FATA-GIM3 which stated that when both tamoxifen and aromatase inhibitor is given in combination it shows better result when both are given individually. CDK4/6 inhibitors in clinical trial have shown its potential in treating the ER-positive breast cancer and also effective against the cells which have developed resistance to the tamoxifen. Drugs under this class are Palbociclib, ribociclib and the trial has shown that when these drugs are given in combination with the fulvestrant or letrozole, has better outcome. Another potential drug on which the studies are conducted are PI3K/AKT/mTOR pathway inhibitor. Alpelisib is a PI3K inhibitor which has a better outcome when given along with the fulvestrant. Everolimus is a mTOR pathway inhibitor which has received FDA approval to treat breast cancer in combination with exemestane. The drugs used in case of HER2+ positive breast cancer was anti-HER2 monoclonal antibody such as trastuzumab and pertuzumab, Antibody-cytotoxic complex such as ado-trastuzumab emtansine and tyrosine kinase inhibitors such as lapatinib which can also cross BBB and can be useful in treating nervous system carcinoma.

The most invasive and difficult to treat TNBC previously had only chemotherapy and surgery as an option as it cannot be treated with targeted therapy, but the recent studies have evaluated the effectiveness of various drugs for treating the TNBC such as PARP inhibitors i.e., Olaparib, EGFR inhibitors such as cetuximab. The effectiveness of immunotherapy to treat TNBC has been evaluated in various studies and pembrolizumab has shown its potential to target cancer cells when given in combination with other drugs such as paclitaxel and carboplatin. Thus, it is very important to understand the sub-type of breast cancer before developing a treatment plan and also different patients will respond differently to different drugs thus keeping in mind the adverse events and the effectiveness of dug in particular patient therapy must be given.

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Conflict of interest

None

9. REFERENCES

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