TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 15
Number 2 *Spring 2022*

78-85

2022

Effective Treatments for Ductal Carcinoma In Situ

Moshe Picciotto

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Moshe Picciotto will graduate with a Bachelor of Science degree in June 2022

Abstract

Ductal Carcinoma In Situ (DCIS) is the most common form of breast cancer wherein its progression interrupts the hormonal receptors and genetic variation of one's DNA. DCIS can be caused by hereditary means, or through mutations. Fortunately, due to the many different modes of contraction, there is a plethora of treatments available in the forms of mastectomy, radiation, chemotherapeutic drugs, and PARP inhibitors, each with their own mechanism of action to combat the tumor and any metastatic effects the cancer may have on the body. This paper analyzes the cancer's mechanism of action upon the body and the positive effects available treatments have to combat the disease.

Introduction

Breast cancer has been affecting 3.8 million women in just the United States alone, making it the most common cancer affecting women in said location. Breast cancer is commonly found in both men and women with an annual 42,500 deaths for women and 2,150 for men. Presuming a woman has not developed breast cancer before the age of 50, the percentage of susceptibility for it jumps up by 25%, resulting that 88 out of 100,000 women can develop ductal carcinoma in situ (DCIS) (Tomlinson-Hansen et al. , 2021). Furthermore, genetics is also a factor as they account for 25% of breast cancer in women under age 30, even though overall genetic mutations only account for 5-10% overall. Also, once a woman becomes post-menopausal there is a 17% increased risk of contraction every five years (Shah ,2014). Based on these jarring statistics, it is not surprising that the probability of a woman developing invasive breast cancer in her life is 12.3% or 1 in every 8 women. Despite these alarming numbers, there are a great deal of modalities to eradicate the cancer and increase life efficacy.

Methods

This comprehensive review is based on critical analyses of literature obtained using various databases available through The Touro College Library online, such as PubMed and ProQuest. The National Center for Biotechnology (NCBI) website was also useful in providing additional source material.

Ductal Carcinoma In Situ (DCIS)

DCIS (Ward et al., 2015), a cancer that occurs in the mammary ducts of the breast, causing the basal myoepithelial layer of the ducts to be filled with malignant cells, accounts for 83% of all cases of breast cancer. Normal breast ducts lead into lobules made of small glandular structures called acini, where there is a bilayer of cells lining this ductal lobular system. They consist of inner luminal epithelial cells and outer luminal myoepithelial cells, where the majority of breast lesions develop, whether benign or malignant. It is deduced that if the tumors remain at this basement membrane, the cancer is still in situ and not invasive (Ward, 2015).

In order to classify the intensity of cancer, five histological grades were established. They are compartmentalized as comedo, cribriform, micropapillary, papillary, and solid. In cribriforming DCIS, the tumor cells fill the duct and form lumen-like projections that appear as hollow protrusions. Micropapillary DCIS histology is characterized by the proliferated cells projecting into the lumen like a bunch of sticks but lack a fibrovascular core. Papillary DCIS, unlike micropapillary DCIS, does contain a fibrovascular core. Cribriform, micropapillary, and papillary in particular are all considered low grade lesions and the odds of developing into an invasive carcinoma are slim. On the other hand, tumor cells that have solid and comedo histological features, which are cells that divide aggressively and have an abnormal appearance, have a greater propensity to become invasive ductal carcinoma.

The spectrum of DCIS is wide with the many different hormone receptors, mitotic pathways, and/or genetic factors that are responsible for the proliferation of the cells, inhibition of tumor suppressor cells, and in some cases anti-apoptotic factors. However, if DCIS is left untreated from the moment of its inception, it would only take up to 2.5 years for it to progress into invasive ductal carcinoma (Tomlinson-Hansen et al., 2021).

Two elements that contribute to any cancer or tumor development are the loss of the TP53 gene and p53 proteins whose function is tumor suppression. If the DNA is not dividing properly, p53 would act against it, either by triggering apoptosis, or activating other genes for cell repair (Sever and Brugge, 2015), subsequently suppressing tumor development. The functionof the TP53 gene is to generate these p53 tumor suppression proteins. Should the TP53 gene be mutated, either through frameshift, missense, or nonsense mutations, it would not produce proper p53 proteins, and thus cell division would proliferate uncontrollably without proper borders (Olivier et al., 2010).

Being that breast tissue is constantly replenishing itself, there are hormone receptors running through it that activate cell division when hormones, namely estradiol-17β (estrogen) and progesterone, bind to their respective hormone receptors. The hormone of interest is then brought inside the nucleus by the hormone-bound receptor and binds to chromatin to initiate gene transcription and protein production. Of all DCIS cases, 75% have an ER (estrogen receptor) dysfunction, denoted as ER+, which

causes an overexpression of cell division, resulting in unregulated cancerous growth (Feng, 2018). Studies have shown that alterations to cyclin D-1, a cell cycle regulator that stimulates the proliferation of cells, is responsible for overexpression. In vitro experiments of breast cancer cells have shown that an influx of estrogen in the blood is clearly correlated with increased cyclin D-1 action or cyclin D-1 mRNA observed in the cell (Fernandez et al., 1998; Zwijsen et al., 1997). There comes a point where the mutant ER will still make cyclin D-1 without there being any estrogen there to activate its transcription (Zwijsen et al., 1997). In fact, the overexpression of cyclin D-1 is so ubiquitous that it is seen in 50-87% of ductal carcinoma cases (Fernandez et al., 1998).

Accordingly, a decrease of estrogen in blood or estrogen-receptor negativity has shown an expected decrease in cyclin D-1 activity in tumor cells. The same decrease in cyclin D-1 has been seen when anti-estrogens were found in the blood, further enhancing the notion that the steroid stimulates cell proliferation. Similar is the case for cyclin-dependent kinase inhibitors p21 and p27, whose job is to repair DNA when the cell cycle is arrested. They appear in abundance when anti-estrogens are counteracting the estrogen, expectantly limiting cyclin D-1 expression (Fernandez et al., 1998).

The important role of epigenetic changes such as aberrant DNA methylation and histone modification in cancer causation, progression, and treatment has been recognized in order to develop the proper therapeutic response to target the transcriptional abnormalities of the cancer. DNA methylation is commonly observed in the binding site at the enhancers of the transcriptional factor Erα in ER+ breast cancer, which would offer insight to the resistance of anti-estrogen chemotherapeutic agents to the binding site (Feng et al., 2018).

Along with the estrogen receptors are progesterone receptors in the breast that can dysregulate the cell cycle. There are progesterone receptors on the cell surface that allow for progesterone to interact with the cell and to partake in the proliferation of the cell with its cell processes and mitotic division. It's supposed to define gene expression, mainly chromatin and genome expression, when it binds to its steroid chemical progesterone. The defect occurs when the cell that produces the progesterone itself is the one that receives. In other words, it goes from paracrine signaling to autocrine signaling (Grimm, Hartig and Edwards , 2016). This may induce migration in early primary tumor cells and, in this way, activate mammary stem cells, thus resulting in uncontrolled cell division and dangerous proliferation (Feng et al., 2018).

Human epidermal growth factor receptor 2 (HER-2) is expressed in many cases of breast cancer. HER-2 expression is regulated by transcription factor AP-2gamma (TFAP2C). This transcription factor is one of the key regulators to hormonal responsiveness in the pathways utilized in breast carcinoma growth. High levels of TFAP2C have been associated with ER+ breast cancer (Wu et al. , 2020). DNA methylation or histone modification also affect this process of excess proliferation of cells, eventually leading to breast tumorigenesis (Feng et al., 2018). In breast cancer specifically, HER-2 is expressed in 50% of in situ carcinomas and eventually ends up in 20% of invasive carcinomas. It is a tyrosine kinase receptor that has an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain. HER-2 heterodimerizes with HER-3 since HER-3 doesn't have any tyrosine kinase activity. Cancer is formed when the HER-2 only homo and not heterodimerizes with HER-3. This affects many downstream signaling pathways associated with breast cancer such as the phosphatidylinositol 4,5-bidphosphate 3-kinase (PI3K)-AKT pathway (Albaghoush and Limaiem , 2020).

The PI3K-AKT pathway is a regulatory pathway for cell proliferation. PI3K is activated by G protein-coupled receptors which in turn translocates protein kinase B (AKT) to be phosphorylated by the plasma cell membrane. A conformational change happens, allowing for two phosphorylating sites to be opened. There is a threonine that is phosphorylated on the N-terminus and C-terminus to be fully active. It is unknown how, but the AKT is transferred to the plasma and nucleus where many of its substrates are located. There is negative regulator phosphatase and tensin homologue (PTEN) which inhibits the activation of AKT. It reduces the amount of PI(3,4,5)P3 produced by PI3K because the PTEN dephosphorylates the products of PI3K. Loss of PTEN either through inactivating mutation or a lack of PTEN in circulation causes more activation of AKT. From there the pathway enhances protein synthesis by phosphorylating mammalian target of rapamycin or mTOR, one of the body's protein synthesis regulators. Activated mTOR promotes cyclin D-1 mRNA production. Cancerous mTOR also inhibits anti-proliferative effects, so it's not only limited to increasing output, but also decreasing regulation as well (Osaki et al., 2004).

Whenever the cause for breast cancer is genetic alterations, it is most likely a mutation in the breast cancer gene, most commonly known as BRCA1 and BRCA2 (BReast CAncer). The genes themselves do not induce cancer, rather they act as tumor suppressor genes in the DNA repair processes such as chromatin remodeling, transcription control, and cell cycle regulation. Their tumor suppressive effects have been attributed mainly to cell cycle checkpoints and DNA repair management.

There are more than 1600 and 1800 known variants of BRCA1 and BRCA2 respectively, the majority of which induce frameshifts, leading to missense or non-functional proteins (Lee et al. , 2020). Thus, deletion mutations and/or loss of function in the BRCA genes lead to decreased DNA repair efficiency and possibly give rise to the expansion of cancerous cells, elevating the risk of developing breast cancer by five to six-fold. Lifelong risk of developing breast cancer through the BRCA1 gene is 65% and with BRCA2 is 45%. Even though BRCA1 or BRCA2 cause 5-10% of breast cancer, 75% of all DCIS cases are due to BRCA1 mutation (Feng et al., 2018).

Triple Negative Breast Cancer

The term triple negative breast cancer (TNBC) is due to the fact that it is ER-, PR-, HER-2-. TNBC accounts for 20% of all breast cancer cases and is most commonly found in women under 40 years old. The overall consensus is that TNBCs have a frequent occurrence of multiple copy-number aberrations involving genes that lead to alterations in multiple signal pathways, which include the mutations/deletions of BRCA1/2 in the DNA repair pathway (Bianchini et al. , 2016). TNBC occurs in 10-15% of sporadic, or non-genetic caused breast cancer, but 66-100% of pathogenic variant BRCA1 breast cancer. In contrast, 14-35% of TNBC cases carry BRCA2 pathogenic variant (Lee et al. , 2020). Breast tumors arising in patients who carry BRCA1 mutations have many molecular features of basal-like sporadic breast tumors, including a greater likelihood of being high-grade, ER/PgR-negative, HER2-negative, and a high frequency of TP53 mutations. The existence of a tight association between BRCA1 mutations, basal-like breast cancer and TNBC has raised the question as to whether BRCA1 loss of function through other mechanisms participates in the pathogenesis of sporadic basal-like breast cancer and TNBC; such an association could be exploited therapeutically with rational clinical trials exploring the role of chemotherapy and biological agents targeting defective DNA-repair pathways (Fernandez , 1998). High grade tissue is observed in TNBCs, with aggressive division and observed necrosis. Such a cancer would not be responsive to treatment used for receptor-positive cancers (Feng et al., 2018). As forkhead box O (FOXO) transcription factors have a recognized role in tumor development and progression, it was shown that FOXO3a expression was highly expressed in TNBC tumors with negative clinical and pathological features, including lymph node metastasis and perineural invasion, and correlated with poor disease-free survival. Due to the severity of TNBC, and limited treatments available for the cancer due to its negative receptor status, an accurate fluorescence in situ hybridization (FISH) assessment is taken so as to not falsely diagnose the cancer (Bianchini et al. 2016).

Risk Factors

Women are prone to breast cancer through certain risk factors. First off, one who has first degree relatives increases one's risk of developing breast cancer compared to those without a family history with a risk factor of 1.69 to 1.37, and the risk increases with the risk increases with the number of first-degree relatives a woman has that had or have breast cancer.

The onset of menarche also is a contributing factor to women developing breast cancer with those whose menarche comes early having a positive-receptor cancer risk by two-fold, while late menarche reduces the risk by 10%.

Early pregnancy has been noted to protect woman from breast cancer. Giving birth at the age of 20, 25,and 30 can reduce the risk of breast cancer by 20%, 10%, and 5% respectively. With breastfeeding, the risk of developing breast cancer is decreased by 4.3% per one year of breastfeeding due to the decrease in endogenous sex hormone levels, which play a role in receptor positive breast cancer (Shah, Rosso, & Nathanson , 2014).

Age at menopause also contributes to the increased possibility of developing breast cancer. The delay of menopause itself per year is a 3% increased risk and 17% every five years (Shah, Rosso, & Nathanson , 2014). (Feng et al., 2018)

Postmenopausal women on hormone replacement therapy exhibit a two to four-fold increase in breast cancer (Kinsinger et al. , 2002).

There are also lifestyle risk factors that increase one's susceptibility to contracting breast cancer such as alcohol, inactivity, and obesity. These risks account for 21% for all breast cancer deaths worldwide. Alcohol consumption of 5-9.9 grams a day has been proven to increase breast cancer risk. Physical, vigorous activity reduces risk by 5%.

If one has had cancer before, and has received radiation therapy for treatment, the previous exposure can eventually lead to DNA mutation leading to DCIS (Shah, Rosso, & Nathanson , 2014).

Testing

There are many tests that are performed to identify if a woman has breast cancer. Self-feeling of something that doesn't belong in the breast, as well as personal observations of how the breast looks can be clear indicators of breast cancer. Signs of breast cancer include finding a new lump in the breast or underarm (armpit); thickening or swelling of part of the breast; irritation or dimpling of

breast skin.; redness or flaky skin in the nipple area or the breast; pulling in the nipple or pain in the nipple area; nipple discharge other than breast milk, including blood; any change in the size or the shape of the breast, and pain in any area of the breast. Ductal Carcinoma In Situ (DCIS) is breast cancer that forms in the milk ducts and accounts for 75-80% of breast cancer found in patients (Memorial Sloan Kettering Cancer Center, 2021).

Close to 90% of breast cancer cases are found via mammogram. The mammogram looks for microcalcifications in the breast, or what is commonly known as dense breasts, mainly to clarify if the density in the breast is just the crowding of cells, or rather the start of a tumor. An MRI is also taken for equivocal findings where breast augmentation prevents effective screening mammography. MRI is also more specific for detecting high risk cancer at .77-.79 as compared to mammography which is only .33-.39 (Shah, Rosso, & Nathanson , 2014). The last test taken is core needle biopsy, to identify which hormone receptors the cancer is positive for, as well as if the cancer utilizes the PI3K-AKT pathway and HER-2 expression (Tomlinson-Hansen et al., 2021).

Surgery

Effective surgery for breast cancer is a mastectomy which is the removal of the full breast. This surgery is curative for 98% of cases and only leaves a 1-2% recurrence rate due to small negative margins or unseen invasive carcinomas. Breast-conserving surgery (BCS) is a surgery that conserves the breast and only removes the cancer within and 2mm of healthy surrounding tissue for negative margin (Tomlinson-Hansen et al. , 2021). The size of the tumor, the location of the tumor, and the quantity of tumors determines which excision the patient will receive. If tumor size is small, but there are many in the breast, it would call for a mastectomy, as well as large tumors would. A small tumor localized in one area would be a candidate for BCS (Ward et al., 2015).

After BCS, radiation therapy will follow to eliminate any residual disease. The NSABP B17 trial demonstrated that in patients who underwent breast-conserving surgery and followed by radiation, there was a 50% to 60% reduction in local recurrence with surgical excision and radiation therapy compared to surgical excision alone (Tomlinson-Hansen et al., 2021). No significant difference in survival rate has been seen down the line with BCS in conjunction radiation therapy at 91.7% when compared to a mastectomy at 92.8%, especially since radiation has its downside of mutating BRCA in DNA repair to alter its normal function (Lee et al. , 2020). The conventional dose of radiation to the whole breast is 45-50Gy (grey) followed by a boost to the lumpectomy bed for an additional 10-16Gy over a 6-week period. If the patient is older than 50, hypofractionation is the preferable treatment which entails less weeks of treatment but more intense waves of radiation that target the exposure of the radiation to normal tissue (Kim & Algan, 2021).

Radiation is significant in disease control. Although radiation therapy has its own drawbacks of possible recurrence, overall, those who had BCS in combination with radiation have only an 8% recurrence rate as opposed to those who had BCS without any radiation therapy whose recurrence rate is at 18.7% (Ward et al., 2015). After 10 years, those who had radiation treatment post-operation have shown a decrease in disease by at least 50% (Alkabban & Ferguson, 2021).

Chemotherapy for HR-positive Treatments

The general effect of chemotherapy treatment in patients post operation has been shown to reduce the risk of recurrence by 50% (Alkabban & Ferguson, 2021). In trials of 5 years of tamoxifen therapy versus no endocrine therapy, the recurrence rate in the tamoxifen group was approximately 50% lower than that in the control group during the first 5 years (the treatment period) and approximately 30% lower during the next 5 years (Pan , 2017). Those with DCIS whose status is hormone receptor positive have a plethora of treatments available for them. Selective estrogen receptor modulators (SERMs) act as agonists towards estrogen receptors in the breast. Though their structure is different than the regular steroidal structure since they have a tertiary structure, that's enough for them to bind to the ligand-binding domain. SERMs include tamoxifen, toremifene, and raloxifene (Adams and McCoy., 2010).

The use of tamoxifen is suggested for hormone positive premenopausal women due its selectivity towards estrogen. Recommended clinical treatment is to take tamoxifen for a 10-year period. Side effects include sexual dysfunction, irregular menstrual cycles, osteoporosis, endometrial cancer, stroke, deep vein thrombosis and pulmonary embolism (Tomlinson-Hansen et al. , 2021).

The outcome of utilizing aromatase inhibitors is to inhibit the cytochrome P-450 component of the aromatase enzyme complex, which is responsible for estrogen and progesterone biosynthesis. It prevents the conversion of androgens into estrogen. There are two types of aromatase inhibitors: Type I and Type II. A Type I aromatase inhibitor is exemestane, whose steroid structure is similar to the androgens and irreversibly inactivates the enzyme substrate binding site of estrogen. Type II aromatase inhibitors are anastrozole and letrozole whose functions

are the same as Type I, but are reversible because their structure is not steroidal. Side effects of aromatase inhibitors are similar to those of SERMs.

Selective estrogen receptor downregulators (SERDs) such as fulvestrant have a higher affinity for the ER than SERMs, but do not display any agonistic activities. It is a novel ER antagonist that binds to the ER to prevent dimerization leading to a rapid degradation and loss of cellular ER expression (Adams and McCoy., 2010).

Oophorectomy

Called a Prophylactic bilateral salpingo-oophorectomy, this surgery removes the ovaries, leading to a major decrease in estrogen produced in the body. It decreases the risks of ovarian cancer by 80% and breast cancer by 50%. This option is mainly considered for post-menopausal women since removal of the ovary would also remove all hormones coming from them which includes reproductive hormones (Kim & Algan, 2021).

Hormone Receptor Negative Treatment

As discussed earlier, the PI3K-AKT pathway's function is to regulate HER-2 to keep control of the cell cycle so that there isn't too much proliferation due to the suppression of tumor inhibitors. Trastuzumab, the first approved drug, is a monoclonal antibody that directly targets the HER-2 protein. It reduces the risk of recurrence and death by 52% and 33%, respectively, if combined with chemotherapy in HER2+ early breast cancer as compared to chemotherapy alone. The most common issue with infusion of cytotoxic chemicals in the blood is the pathway of delivery. The chemicals are delivered through a glomerular filtration, thus increasing the toxicity of the blood and weakening the kidneys (Alkabban and Ferguson , 2021).

After treatment of Trastuzumab, it is necessary to follow up with a combination of cytotoxic chemical agents that combine for a stronger effect. These chemicals provide the body with an ability to overcome the cancerous cells by disturbing the cancerous cell cycle (Carlson et al., 2009)

Doxorubicin is an anthracycline derived from the streptomycin bacteria which is from the group of polyketides (Ridley and Khosla , 2009). Anthracyclines function in halting protein synthesis by attaching to the 16s DNA chain of the smaller 30 chain polypeptide thus preventing anything else from attaching and arresting cell cycle function (Waters and Tadi, 2021).

Cyclophosphamide is a type of nitrogen mustard drug which exerts its effects through the alkylation of DNA. The drug is not cell-cycle phase-specific and metabolizes to an active form capable of inhibiting protein synthesis through DNA and RNA crosslinking. The majority of the antineoplastic effects of cyclophosphamide are due to the phosphoramide mustard formed from the metabolism of the drug by liver enzymes which hydroxylate, metabolize, and then cleave into alkylating agent phosphoramide mustard and acrolein. The phosphoramide metabolite forms cross-linkages within and between adjacent DNA strands. These modifications are permanent and eventually lead to programmed cell death (Ogino and Tadi , 2021).

Fluorouracil is an antimetabolite, acting as a competitive inhibitor towards DNA synthesis. It is a homologue that looks like the base uracil but has a fluoro group on its fifth carbon instead of a hydrogen. This prevents the conversion of deoxy-uridylic acid to thymidylic acid, halting DNA synthesis and cell division (National Center for Biotechnology Information , 2022). The main issue is that it does not differentiate between fast growing cells and cancerous cells, therefore it will attack all fast-dividing cells, such as hair follicles, blood cells ,mouth, stomach, and bowel cells (Mayo Clinic, 2021).

The Taxanes Docetaxel and paclitaxel, also known as Taxol, are mitotic inhibitors that act as a spindle poison to inhibit microtubule dynamics and arrest the cell cycle. Docetaxel exerts 1.2-2.6 stronger cytotoxicity than paclitaxel, and 1000 times greater than cisplatin (Katsumata , 2003).

Cisplatin is a platinum based chemotherapeutic agent that can form bonds with the polar ends of DNA due to platinum's positive charge. In particular, use of cisplatin therapy has been suggested for TNBC harboring a BRCA mutation. Cisplatin is a DNA-intercalating agent that cross-links DNA resulting in interference with RNA transcription and DNA replication activities. If the DNA lesions are not repaired, DNA-damage induced cell-cycle arrest and apoptosis are triggered. Cells can become resistant to cisplatin by several mechanisms including change in the accumulation of the drug in cells either by inhibited uptake or enhanced efflux, detoxification of the drug by redox mechanisms, repair of the DNA by excision repair mechanisms, or negative regulation of apoptotic mechanisms. Carboplatin was developed as a less toxic version of cisplatin, and also as a chemical with a longer half-life, but 90% would be excreted with urine (Hill et al., 2019).

Regarding the PI3K-AKT pathway, the initial treatment available was Wortmannin which inhibits the PI3K-AKT pathway thus promoting apoptosis. It was found that the main function of Wortmannin was that it prevented the phosphorylation of the AKT protein. But, due to its organic makeup which prevents is not soluble in water, Wortmannin was discontinued for clinical trials. LY294002, a water soluble Wortmannin, was developed but its PI3K inhibitive ability was reduced. LY294002,a

pro-apoptosis and anti-proliferative chemical reagent is a competitive and reversible inhibitor to the ATP binding sites of PI3K, as well as suppresser of tumor growth (Osaki et al., 2004).

One combination found to increase recovery after receiving treatment with trastuzumab is doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel. Another is docetaxel and cisplatin (Carlson et al., 2009)

TNBC Treatment

For TNBC, the cancer is not generated through any hormonal response as its name suggests, therefore, it will require chemotherapy that will halt DNA replication. Poly (ADP-ribose) polymerases (PARPs) attach to single strand DNA breaks and intracellularly signals to nuclear repair proteins to fix the DNA. In cancerous cells, PARP reacts to repair a single stranded cell, but due to the inability of BRCA to heal double DNA strand breaks, the cell continues to divide damaged DNA. PARP inhibitors deactivate the PARP from reacting to the single strand breaks which would then lead to replication fork damage, thus causing the cell to program cell death (Lee et al. , 2020) (Feng et al., 2018).

Other forms of treatment for TNBCs include injection of the cytotoxic chemicals as mentioned by hormone-negative breast cancer. Surprisingly, although TNBC has the most limited options for treatment, it has the highest response rates to neoadjuvant chemotherapy. Approximately 30–40% of patients with early-stage TNBC treated with standard neoadjuvant anthracycline and taxane-based chemotherapy regimens achieve a pCR (pathogenic complete response) after treatment (Feng et al., 2018). A combination of a taxane and anthracyclines remain as important chemical agents needed for treatment. Adding carboplatin to paclitaxel followed by a dense dose of doxorubicin and cyclophosphamide has an increased pathogenic complete response from 46-60% due to the added cisplatin. Platinum based agents really help in BRCA1/2 mutations with a response rate of 75% (Feng et al., 2018).

Discussion and Conclusion

Due to the differences in the different cancer types, concocting a treatment utilizing each chemotherapeutic agent would not have the potency to effectively treat the patient. On the other hand, a PARP inhibitor would be something that all cancers whether hormone receptor positive or negative can benefit from. Even when the cancer is ER+ and/or PR+, the main result would still be a halting of DNA synthesis. The only issue is whether it would be effective for hormone receptor positive cancers. Hormone receptor positive breast cancers would prefer tamoxifen and AIs because they directly addresses the problem, and they will react swiftly and target the estrogen causing the issue. There is research that when insulin was pumped into MCF-7 breast cancer cells followed by a cytotoxic chemotherapeutic regimen, the pCR was higher because there was a greater absorbance of the chemicals, the cross-membrane channels have expanded permeability due to the GLUT 1 and 3 transporters. The pathway travelled is the PI3K-AKT pathway. Therefore, any injection of insulin can indeed enhance responsiveness to the chemotherapy treatment plan for whichever cancer is found while also reducing toxicity due to glomerular filtration(Agrawal et al., 2017). A way that usage of cytotoxic chemicals can be used even for HR+ breast cancer is to use a taxane pre-operation to shrink the size of the tumor before excision. This can further reduce the need for a mastectomy and instead one can proceed with a lumpectomy (National Cancer Institute, 2022).

Essentially, breast cancer is something that can affect one's life either through hormonal avenues, specific homeostatic pathways, or genetic aberrations. Conveniently, as many as there are variations of sickness there are as many methods of treatment, either through surgery, radiation, chemotherapeutic drugs, cytotoxic chemicals, or PARP inhibitors, each utilizing their own method of warfare to combat the body's ailments. Through our analysis of the disease and methods of treatment, we can provide treatment to aid in safe and healthy recovery.

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