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Recent Advances in Breast Cancer Treatments

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ABSTRACT

Breast cancer is one of the deadliest cancers. Some of the therapies that target breast cancer include surgery, chemotherapy, hormonal therapy, gene therapy, immunotherapy, and radiation. Newer treatment types introduce new ideas and technologies that are fostering new breast cancer treatments. However, breast cancer is a complex disease that ranges in severity and pathology, thereby making a universal treatment elusive. Current strategies to treat breast cancer involve combining multiple therapies. In this review article, I will describe the evolution of breast cancer treatments and its upward trajectory towards finding a cure.

Overview of Breast Cancer

The most common type of cancer of women in the United States is breast cancer. It is estimated that 1 in 8 women will develop breast cancer in their lifetime. Breast cancer is also the second most common type of cancer in the United States, after skin cancer. The American Cancer Society estimates that there will be 281,550 new cases of invasive breast cancer in 2021 and 43,600 women will die from breast cancer in 2021 (American Cancer Society, 2021). The financial impact of breast cancer treatment is also significant. In a study done by Allaire *et al.* It was shown that it costs $52,524 per year, excluding lost expenses from time spent not working (Allaire et al., 2016). Treatment prices, however, can vary based on the type of breast cancer, and individual circumstances related to each patient.

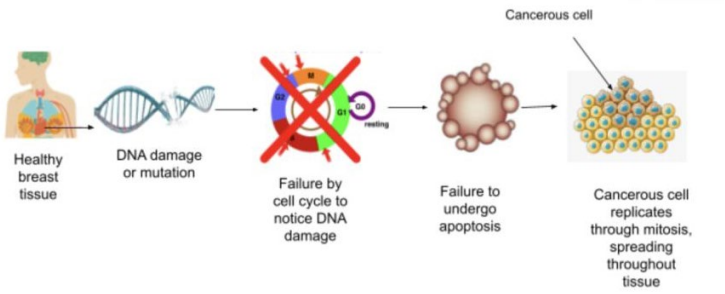

Figure 1. Mechanism of Breast Cancer Formation. Healthy cells undergo DNA damage and reproduce uncontrollably producing cancer cells.

Breast cancers can be classified by their grade, stage, and receptor status. Many times, after seeing a mass on an X-Ray, doctors will take a biopsy to evaluate under a microscope. The grade that the cancer is given is based on how differentiated the cancerous cells look versus healthy cells. This includes looking at the size and shape of the cells and their organelles or the arrangement of cells. The more poorly differentiated the cells, the higher the grade

given to the cancer. Stage is also important with regard to classifying tumors by determining the size of the tumor and whether the tumor has spread beyond the breast, potentially involving lymph nodes or other organs in the body (metastatic disease). This method of categorizing breast cancer is known as the TNM system and helps determine how aggressive the tumor is, and how far it has spread at a particular point in time. The receptor status for breast cancer is

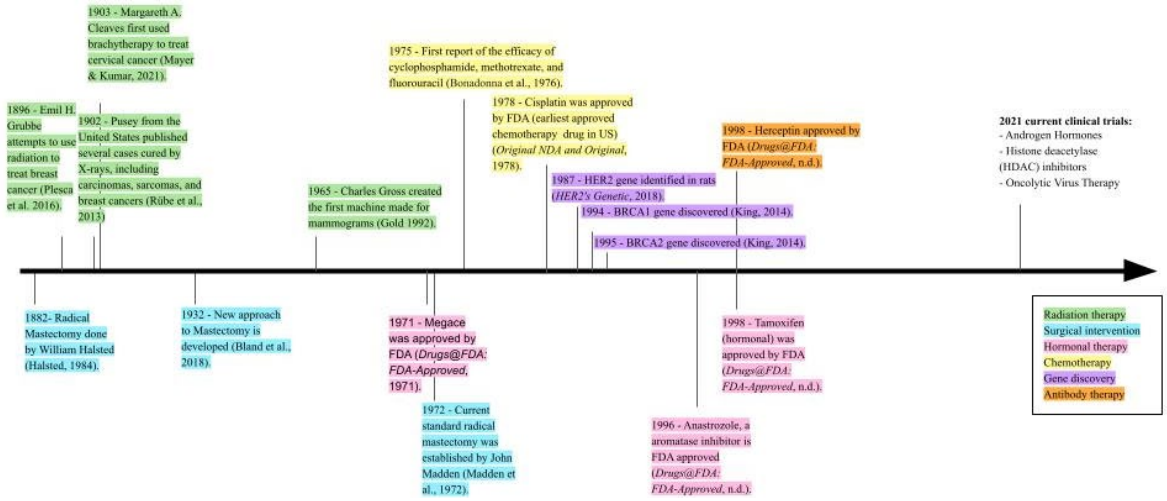

Figure 2. Milestones In Breast Cancer Treatment. A timeline visually representing how breast cancer treatments have evolved over time.

also important in determining how to best treat the disease. First, there is hormone receptor positive breast cancer. This type of breast cancer needs the hormones estrogen or progesterone or both to grow. Although estrogen receptor positive breast cancer tends to grow slowly, the cancer may recur years after being treated. Hormone receptor negative breast cancer do not have estrogen or progesterone receptors and are most found in post-menopausal women. This type of breast cancer grows rapidly and cannot be treated with hormone therapy drugs. Triple positive breast cancer has estrogen receptors, progesterone receptors, and the HER2 gene which is linked to a more severe kind of breast cancer. In contrast, triple negative breast cancer does not have hormone receptors and instead is caused by a mutation in the BRCA1 gene (Figure 1). This particular form of breast cancer tends to be very aggressive as it grows and spreads rapidly. Hormone therapy is ineffective in this form of cancer, the treatment options are therefore limited.

Breast Cancer Treatment Types

The specific type of breast cancer helps oncologists to determine which treatment has the best chance of being effective. Presently there are numerous ways to help treat breast cancer. This includes surgery, chemotherapy, hormonal therapy, gene therapy, immunotherapy, and radiation (Figure 2). Often patients require a combination of several different therapies in order to maximize the chance of remission. The possibilities are endless, and new treatments and therapies are always on the horizon.

Surgery

The first known treatment for breast cancer was William Halsted's radical mastectomy procedure which was first performed in 1882. The operation included removing the mammary gland, pectoral muscles, and all of the axillary lymphatic tissue. The goal was to remove all possible cancerous cells and prevent the spread of cancer cells. This

technique was effective but was extremely traumatic to the body, with numerous serious complications. Some examples include damage to the chest wall and or pneumothorax, paraesthesia, and lymphedema of the arm (Plesca et al., 2016). The surgery seriously impacts the quality of life for the patients. Despite its limitations, this procedure was life saving for many women around the world, and was often successful in clearing the body of cancer.

In order to make the mastectomy less traumatic to the body, David Patey and W.H. Dyson modified Halsted's radical mastectomy in 1932. The major difference between the two techniques was that the modified mastectomy did not remove the pectoralis major muscles. The reason why Patey and Dyson believed it was feasible to not include the removal of the pectoralis major was because the vast majority of breast cancers do not typically involve the pectoralis major. Although this procedure was somewhat less invasive than the radical mastectomy there were other new complications. This modified radical mastectomy requires a large incision, which is difficult to close. Surgeons often need to perform skin grafts in order to close the incision which leads to an increased risk of infection and scarring (Patey & Dyson, 1948).

In 1972 John Madden created a new surgical technique to treat women with breast cancer. Instead of making a wide incision like Patey and Dyson, Madden performed an elliptical incision which arched around the top of the areola and within the inframammary fold. This procedure enabled the surgeon to remove nearly all the mammary tissue, without having to create a large incision. This procedure was better tolerated by patients and did not require skin grafts.

During the last 25 years the surgical techniques have continued to evolve. Currently, many breast cancers are now surgically treated with a procedure called a lumpectomy. In this procedure the surgeon removes the tumor, leaving the otherwise normal breast tissue intact (Berg, 1984). This procedure can be very effective in removing the cancer, but is far less invasive. Patients can therefore be properly treated, with less complications and a better cosmetic outcome.

Plastic surgeons are now frequently involved in the care of breast cancer patients. The plastic surgeons often work in combination with breast surgeons to achieve two goals. The primary goal is to remove the cancer, the secondary goal is to achieve a positive cosmetic outcome. This may include breast reconstruction procedures. This can be very psychologically important to women trying to recover from breast cancer.

Radiation

In 1895 Wilhelm Conrad Roentgen discovered X-rays, this revolutionized research and science decades. X-rays could be used to see inside of humans without a scalpel. However, after taking an X-ray, tissue burns would be left where the X-Ray was taken. Emil H. Grubbe was the first person to think of using these new, burning rays in a completely new way: to “burn out” cancer. On January 29, 1896, one of Grubbe’s professors allowed him to use the X-Rays to try to help a patient suffering with recurring breast carcinomas. The initial treatment proved successful, but 17 sessions later, the radiation was too much for her body and she succumbed to the treatment. One of the main issues with large amounts of radiation is that it damages not only cancerous cells, but also healthy cells (Plesca et al., 2016).

Years later William Pusey published a paper showing that targeted radiation can be used to help treat a variety of cancer patients, including breast cancer and was the first person to successfully apply radiation to cure cancer (Pusey, 1905).

Today radiation oncologists are able to direct the radiation to a very small target. This is designed to destroy the cancer cells, but leave the adjacent normal tissues unharmed. Radiation is now commonly used in addition to surgery and/or chemotherapy to treat breast cancer.

The understanding of radiation also led to the creation of diagnostic radiology. Radiology enables doctors to non-invasively visualize the human body, and help diagnose and treat patients. Doctors routinely utilize X-rays, mammograms, CAT scans and PETS scans to help diagnose and treat their patients. All of these modalities are based upon a fundamental understanding of radiation. These tests have become crucial to the health care system.

Hormonal Therapy

The hormone progesterone was being experimented with in the early 1950s to treat breast cancer but only had minor success. The first truly successful treatment was megestrol acetate in 1971. Megestrol acetate was progesterone based, and because progesterone has antiestrogenic effects, it would help block estrogen from attaching to cancerous cells, and therefore impede the effects of estrogen on the cancer cells. As with all medications, there were issues. The most common side effect is weight gain but overall the drug was a success.

The Importance of Estrogen Receptors

In breast cancer, estrogen binds to cancerous cells and fuels cancer growth. Megestrol acetate is composed of the hormone progesterone. Progesterone has antiestrogenic effects, meaning that it acts as a competitive inhibitor with estrogen so that cancerous cells cannot receive estrogen. This then slows and blocks breast cancer reproduction.

The birth of aromatase inhibitors was one of the next breast cancer treatment breakthroughs. In 1996, aromatase inhibitors were introduced as another form of hormonal therapy. Aromatase inhibitors inhibit the enzyme aromatase. This enzyme is responsible for distributing estrogen to receptors so blocking its function blocks the spread of breast cancer.

Twelve years later in 1998, Tamoxifen was created by Dora Richardson, another hormonal drug, was approved by the FDA (Quirke, 2017). Tamoxifen works by using estrogen competitive inhibition. In estrogen receptor positive breast cancer, estrogen binds to cancer cells producing cells which promotes cancer growth. Tamoxifen binds to this receptor before estrogen can, which inhibits cell growth, killing the cancer cells. This treatment is extremely effective, however only works for women with estrogen receptor positive breast cancer. Despite this, Tamoxifen has been revolutionary and is still one of the most common drugs women use to treat breast cancer.

Chemotherapy

Chemotherapeutic drugs work by interfering with DNA replication, stunting the growth of cancer cells. The first time chemotherapy was used was in 1975 Specifically, cyclophosphamide, methotrexate, and fluorouracil (CMF) showed clinical improvement in helping to treat women with node positive breast cancer. CMF was the first of its kind, this opened the world to a whole new family of medicines to help treat breast cancer.

Cisplatin, the next main chemotherapy drug approved by the FDA, was not related to CMF. Cisplatin was first created by Barnett Rosenberg and was approved for use in the FDA by 1978 (Original NDA and Original, 2021). It was created accidentally after Rosenberg inadvertently realized that cisplatin halted cell division (Rosenberg, Vancamp, Trosko, Mansour, 1969). Cisplatin works by forming intra-strand crosslinks with purine bases within DNA. This interferes with DNA replication and repair (resulting in cell damage) ultimately causing apoptosis (Marosi, 2017). Despite its powerful influence upon cancer cells often these cells ultimately develop resistance, and the benefit becomes muted. Despite this limitation cisplatin is often one of the most effective in treating patients with triple negative breast cancer.

Cyclophosphamide contains metabolite phosphoramide mustard which is only formed in cells with low levels of aldehyde dehydrogenases enzymes (ALDH). Phosphoramide mustard forms DNA crosslinks, both in between and within DNA strands at guanine N7 positions. This change causes apoptosis of cancer cells due to DNA damage. Unfortunately, sometimes the DNA may be repaired, making the drug ineffective (Clark & Palle, 2016).

Methotrexate is an antimetabolite which means it inhibits use of a metabolite (something used in metabolism). It competitively inhibits dihydrofolate reductase which works in synthesizing tetrahydrofolic acid. Tetrahydrofolic acid normally helps synthesize amino acids and nucleic acids. Inhibition related to methotrexate disables cancer cells from the ability to reproduce, ultimately resulting in apoptosis and cell death (Rajagopalan et al., 2002).

Flououracil acts as a thymidylate synthase (TS) inhibitor. TS normally synthesizes the pyrimidine thymidylate (dTMP), a required nucleotide for replication of DNA. With this enzyme being inhibited, DNA replication cannot occur properly. Inhibiting DNA replication prevents breast cancer cells from growing. Fluorouracil is one of the few treatments effective in treating patients with triple negative breast cancer (Álvarez et al., 2012).

Drawbacks of Chemotherapy

Chemotherapy drugs target cells that are fast as growing and reproducing. As a result, a common side effect is that it damages normal cells that typically reproduce rapidly. This includes hair cells, and the cells that line the gastrointestinal tract. These treatments often lead to hair loss and gastrointestinal symptoms such as diarrhea. Chemotherapeutic agents also have a deleterious effect on the immune system, making patients more vulnerable to infections. And finally, fatigue is also very common in patients receiving chemotherapy.

Gene Discovery and Antibody Therapy

Gene discovery has had a major impact on creating treatments available for patients with breast cancer. In 1987, Dennis Slamon and his colleagues discovered HER2, a growth factor receptor gene. This gene encodes a cell-surface receptor that causes cells to grow and divide uncontrollably. When the HER2 receptor levels are elevated in women with breast cancer, these patients tend to have a worse prognosis, with higher rates of metastatic disease, recurrences, and death (Slamon 1987). Now that scientists have identified this gene and protein, they can now try to create and try to inhibit their function.

Another gene closely linked to breast cancer is the BRCA1 gene. In the early 1990's Mary-Claire King, a geneticist at University of California, Berkeley first hypothesized that a gene on chromosome 17 could be linked to the development of breast cancer. In 1994 scientists at Myriad Genetic sequenced the BRCA1 and BRCA2 genes on chromosome 17. Alterations of these genes have shown a strong link to developing breast cancer (King, 2014). Mutation in BRCA1 and BRCA2 can be inherited, but advances in gene sequencing technologies allows scientists to identify affected individuals and work to prepare treatments to block the transcription of this gene.

In 1998, the FDA approved the drug Herceptin which was developed by Genentech, a large biopharmaceutical company (Siegel, 1998). Herceptin is an antibody that blocks the function of the HER2 receptor. Initially, Herceptin was used for women with metastatic breast cancer. This however has evolved over time and is now commonly used in combination with other agents to also treat women without metastatic disease (Bange, Zwick, & Ullrich, 2001). The development of Herceptin was a milestone in the search to cure breast cancer and will hopefully help to inspire new antibody therapy treatments in the future.

Treatments In Clinical Trials

Androgen Hormones

Androgen hormones can be used to fight ER positive and some forms of ER negative breast cancer (Giovannelli et al., 2018). In ER+ breast cancer, androgen hormones work by acting as a competitive inhibitor to estrogen. As explained earlier, ER+ breast cancers are stimulated by the binding of estrogen to receptors on cancer cells. Inhibition of this process will limit cell growth and reproduction (Peters et al., 2009). As expected, there are drawbacks to this treatment. For example, in patients with HER2+, ER–, and Androgen Receptor (AR) +, androgen hormones can actually stimulate cancer growth (Giovannelli et al., 2018). However, this type of competitive inhibitor is effective and overall is a promising drug.

Histone Deacetylase (HDAC) Inhibitors

HDAC inhibitors treat ER+ breast cancer (Romero, 2019). They work by methylating certain parts of DNA and modifying histone to make the cancerous DNA inaccessible during DNA replication. Additionally, deacetylation may prevent the binding of transcription factors, blocking DNA synthesis. Also, HDAC inhibitors may regulate transportation of apoptotic genes, influencing cell death. It may also increase cell cycle genes that block the formation of dimers and cyclin kinases to increase apoptosis. One major benefit of this treatment is that epigenetic changes are reversible (Eckschlager, 2017). Therefore, if the side effects are severe, or the treatment is not working well, the negative effects can be reserved.

Oncolytic Virus Therapy

An adenovirus can be used to treat TNBC and +-HER2 breast cancer (Marra, et al., 2014). Researchers are now able to place an immune supporting plasmid in the adenovirus 'oncolytic virus genome. The altered adenovirus then reproduces and releases immune regulatory factors which can help fight the cancer cells. Although currently in clinical trials only, there have been promising results in lab animals making this treatment a promising new form of therapy that will open a door to an entirely new area of research (Zhu et al., 2012).

The Future of Breast Cancer Treatment

The "perfect" breast cancer treatment does not currently exist. The perfect treatment would not only treat cancer, but cure it. The treatment would be with little to no side effects, allowing patients to maintain a good quality of life. It would also be great for treatments to work quickly and non-invasively so patients can return to usual activities without disruption. And finally, it would be great if treatments were affordable and easily available to all of those in need. This includes limiting doctors appointments and necessary days of rest. Of course, these features would be amazing but are not yet entirely realistic. The scientific progress that has occurred during the past 100 years is astonishing. Breast cancer is now a treatable disease, and many breast cancer patients are now able to live long fulfilling lives long after being diagnosed. The keys to fighting breast cancer are twofold. One is early detection with screening exams such as mammography, ultrasound, and MRI. The second of course is to continue developing new therapies that are specifically designed to treat all of the different variations of this complex disease. These therapies will not be created in the blink of an eye, but with the new research and technologies being created, each day we are one step closer to discovering this life changing treatment.

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