The Journey to Discover the Next Magic Bullet

Introduction

According to the American Cancer Society, the oldest description of cancer "was discovered in Egypt and dates back to about 3000 BC. It's called the Edwin Smith Papyrus and is a copy of part of an ancient Egyptian textbook on trauma surgery. It describes eight cases of tumors or ulcers of the breast that were removed by cauterization with a tool called the fire drill. The writing says about the disease, 'There is no treatment.'" ("Early History of Cancer") . Breast cancer is currently the most common cancer among women worldwide. In the United States alone, it is estimated that nearly three hundred thousand women will develop some form of breast cancer in 2014 and forty thousand breast cancer deaths ("Breast Cancer Statistics"). Some cancers are inherited, while others result from a chain of gene mutations in cells ("Genes and Cancer") .

It will be quite difficult, if not impossible, to find a single cure for not only breast cancer, but other cancers as well. Some cancers such as HER2-positive cancers are more aggressive than others, such as estrogen receptor positive cancers, which makes it difficult to find a specific type of medicine that will eliminate cancers altogether. For most breast cancers, there are a variety of different treatments used to help eliminate the cancer cells, such as chemotherapy, hormone therapies, and target therapies. The majority of breast cancers are carcinomas, meaning the cancer cells originate in the lining layer of organs such as the breasts. Rarely are breast cancers sarcomas, meaning the cancer cells originate in connective tissues such as muscle tissues, fat tissues, or blood vessels. However, cancer cells may travel through the blood stream to other areas of the body "where they begin to grow and form new tumors that replace normal tissue" in a process called metastasis ("Breast Cancer Overview") .

Paul Ehrlich, a famous physician from the early 1900s, worked in a bacteriology lab under Robert Koch looking to find a chemical that could not only attach itself to particular germs but also kill it. He called these chemicals 'magic bullets' ("Magic Bullet") . Perhaps a new "magic bullet" will be discovered that could help lead us to a cure for not only breast cancers, but also provide a link to discovering a cure for other cancers as well.

Gene Mutations

"Cancer begins when genes in a cell become abnormal and the cell starts to grow and divide out of control" ("Genes and Cancer") . After genes mutate, they are supposed to either be fixed, or are subjected to apoptosis, otherwise known as cell suicide. If the cell does not do one of those two things, a person may develop cancer. However, in order for cancerous cells to develop, more than one mutation often occurs. These mutations affect a gene involving cell division or a gene that normally causes a defective cell to die. Gene mutations can either be inherited or acquired. An inherited gene mutation is present in the egg or sperm that forms the child, which is passed on to each generation of cells. "This type of mutation is also called germline or hereditary. Inherited mutations are thought to be a direct cause of only a small fraction of cancers" ("Genes and Cancer") . On the other hand, acquired mutations cause most cancers and are more common. While an inherited mutation is present in the zygote, an acquired mutation is developed later on in life. "This type of mutation is also called sporadic, or somatic" ("Genes and Cancer") .

Mutations do not always occur as a result of old age. There are many environmental factors that play a role in development of cancer, as well as aging. "Chemical and physical agents that damage DNA in such a way as to cause an increased rate of mutation are called

mutagens. Many known mutagens can increase the risk of cancer and are known as carcinogens. People who have had heavy or prolonged exposure to carcinogenic agents, which include chemicals, ultraviolet light, and other forms of radiation, are more at risk of developing cancer than those who have not been exposed" (Parham 492) . "Chemical carcinogens tend to cause mutations due to single nucleotide substitutions in DNA. Radiation, in contrast, tends to produce grosser forms of damage such as DNA breaks, cross-linked nucleotides, abnormal recombination, and chromosome translocations" (Parham 492) . Also, overexposure to ultraviolet radiation from the sun has become an increasing problem over the years that has led to skin cancer. Another interesting factor that may result in mutations are viruses. Certain viruses have the potential to transform cells by setting up chronic infections in those cells and "producing novel virally encoded proteins that override or interfere with the cell's normal mechanisms for regulating cell division. Infected cells therefore start to proliferate" (Parham 492) . With that being said, we do have DNA repair mechanisms in our cells that are supposed to fix these mutations that occur.

The first step is to compare tumor cells to normal tissue to see what genes have been mutated. "Several genes are known to be responsible for conferring the susceptibility to breast cancer" (Chitrala and Yeguvapalli 1) . "Studies show that fifty one variants in 40 genes are significantly associated with breast cancer risk and among them variants in six genes i.e., BRCA1, BRCA2, TP53, PTEN, STK11, and CDH1 show strong association" (Chitrala and Yeguvapalli 1) . "tP53 is one of the major genetic risk factors which is known to be mutated in many of the breast tumor types" (Chitrala and Yeguvapalli 1) . "The p53 protein functions as a sequence-specific transcription factor to regulate key cellular processes, including cell-cycle arrest, DNA repair, apoptosis, and senescence in response to stress signals. p53 is maintained at a

low level in the cell, but becomes rapidly stabilized and activated in response to DNA damage, hypoxia, hyperproliferation, and other types of cellular stresses" (Scoumanne, A) . This tumor suppressor protein is ultimately supposed to prevent cancer cells from growing ("Genes and Cancer") . When there is little to no p53 to regulate genome mutations, more mutations are likely to occur; therefore, development of cancer will be more likely to occur.

Cancer Therapy Types

Hormone Therapies

While proteins such as p53 are meant to prevent the growth of cancer cells, other hormones such as estrogen and progesterone promote the growth of cancers that are hormone receptor positive ("Hormone Therapy for Breast Cancer") . "Hormone receptors are proteins found in and on breast cells that pick up hormone signals telling the cells to grow" ("Hormone Receptor Status") . For instance, if a cancer is estrogen-receptor-positive (ER+) then it has receptors for estrogen. "This suggests that the cancer cells, like normal breast cells, may receive signals from estrogen that could promote their growth", and likewise with cancer that is progesterone-receptor-positive (PR+) ("Hormone Receptor Status") . Hormone-receptor status is one of the main characteristics of breast cancer that doctors will investigate in order to choose the right treatment for their patient. If the cancer does happen to be estrogen-receptor-positive or progesterone-receptor-positive, then a doctor may choose hormonal therapy, which is sometimes called anti-estrogen therapy. Hormonal therapy "works by lowering the amount of estrogen in the body or blocking estrogen from attaching to the breast cancer cells" ("Hormone Receptor Status") . There are a few main types of hormonal therapy that are used, which include selective

estrogen-receptor response modulators (SERMs), aromatase inhibitors, estrogen-receptor downregulators (ERDs), luteinizing hormone-releasing hormone agents (LHRHs), and even prophylactic ovary removal.

"SERMs work by sitting in the estrogen receptors in breast cells. If a SERM is in the estrogen receptor, there is no room for estrogen and it can't attach to the cell" ("Selective Estrogen Receptor Modulators") . This means that the cell will not receive a signal from estrogen to grow and multiply. SERMs are selective, meaning that a SERM that "blocks estrogen's action in breast cells can activate estrogen's action in other cells, such as bone, liver, and uterine cells" ("Selective Estrogen Receptor Modulators") . There are three SERMs, which include Tamoxifen in pill form, Evista, and Fareston. Tamoxifen is the most prescribed and most well known SERM. It was FDA approved in 1984. While taking SERMs such as tamoxifen combined with other therapies such as aromatase inhibitors can reduce the risk of the cancer returning, SERMs may potentially cause some serious side effects, including blood clots, strokes, and endometrial cancer. Other common side effects of SERMs include fatigue, hot flashes, night sweats, vaginal discharge, and mood swings ("Selective Estrogen Receptor Modulators") .

"Aromatase inhibitors stop the production of estrogen and work by blocking the enzyme aromatase, which turns the hormone androgen into small amounts of estrogen in the body" ("Aromatase Inhibitors") . It is important to note that since aromatase inhibitors cannot stop the ovaries from making estrogen, aromatase inhibitors only work in postmenopausal women. Like SERMs, there are three aromatase inhibitors, which include Arimidex, Aromasin, and Femara. These drugs were FDA approved by the end of the 1990s. Unlike SERMs, aromatase inhibitors cause fewer serious side effects, but can cause heart problems, osteoporosis, and more broken bones than Tamoxifen at least for the first few years of treatment. The most common side effects

of aromatase inhibitors are joint stiffness and joint pain. It is very important to note that if this is a path a doctor and patient chooses, it may be necessary to also take bone-strengthening medicine due to the known aromatase inhibitor side effects ("Aromatase Inhibitors").

ERDs block the effects of estrogen in breast tissue. ERDs are very similar to SERMs in that they sit in the estrogen receptors in breast cells so estrogen cannot attach itself to the cell. In addition to this, ERDs also "reduce the number of estrogen receptors and change the shape of breast cell estrogen receptors so they do not work as well" ("Estrogen Receptor Downregulators") . The only ERD available for hormone-receptor-positive breast cancer is Faslodex, which essentially breaks down estrogen receptors so estrogen cannot latch on. Some of the common side effects of Faslodex include hot flashes, gastrointestinal issues, back pain, and headaches ("Faslodex") .

"LHRHs shut down the ovaries and stop them from producing estrogen, which means less estrogen is available to help support the growth of hormone-receptor-positive breast cancer" ("Hormone Receptor Status") . Examples of LHRHs include Zoladex, Lupron, and Trelstar. When the treatment is stopped, the ovaries may begin functioning again. The only people who may receive this treatment are premenopausal women with early stage, hormone-receptor-positive breast cancer ("Hormone Receptor Status") .

However, if the cancer is hormone-receptor-negative, hormonal therapy is unlikely to work. If this is the case, other therapies such as targeted therapies, chemotherapy, or radiation therapy may work.

Targeted Therapies

When therapies such as hormone therapies are not effective, targeted therapies may be a better approach. "As researchers have learned more about the gene changes in cells that cause cancer, they have been able to develop newer drugs that specifically target these changes" ("Targeted therapy for breast cancer") . These drugs often have less severe side effects than chemotherapy drugs. Targeted therapies have proven more effective for HER2-positive cancer patients. "HER2-positive breast cancer is a breast cancer that tests positive for a protein called human epidermal growth factor receptor 2, which promotes the growth of cancer cells" ("HER2-Positive Breast Cancer") . About 1 in 5 people who have breast cancer are HER2-positive. This is due to the cancer cells making an excess of HER2 because of a gene mutation ("HER2-Positive Breast Cancer") . This specific gene mutation, along with the elevated levels of HER2 that it causes, occurs in many types of cancers, not just breast cancer. "All cells have HER2 receptors, including healthy cells and cancer cells. In HER2-positive cancer, tumor cells have more HER2 receptors than normal, and too much HER2 makes these cancer cells grow and divide too rapidly" ("Understanding HER2-Positive Breast Cancer") . This may explain why this mutation is found in cancers from different areas of the body other than the breasts, such as the lungs, ovaries, stomach, and pancreas. However, not as much research has been done on these in regards to HER2, because it is not nearly as common as HER2-positive breast cancer. Perhaps performing more research on HER2-poitive breast cancers may help future research on the other HER2-positive cancers. This mutation, unlike others, cannot be inherited from a parent.

There are four tests that can determine the HER2 status of cancer cells. The IHC test (ImmunoHistoChemistry) "finds out if there is too much HER2 protein in the cancer cells"

("HER2 Status") . The FISH test (Florescence In Situ Hybridization), the SPoT-Light HER2 CISH test (Subtraction Probe Technology Chromogenic In Situ Hybridization), and the Inform HER2 Dual ISH test (Inform Dual In Situ Hybridization) "find out if there are too many copies of the HER2 gene in the cancer cells" ("HER2 Status") .

HER2-positive cancers tend to be more aggressive than other types of breast cancer. HER2-positive cancers also tend to be estrogen-receptor-negative and are typically not very responsive to hormonal treatment. Treatments that specifically target HER2 have proven very effective over the past several years. Several drugs have been developed that target this HER2 protein.

Trastuzumab, also known as Herceptin, specifically targets HER2 and "kills these cancer cells and decreases the risk of reoccurrence. Trastuzumab is often used with chemotherapy, but it may also be used alone or in combination with hormone-blocking medications such as an aromatase inhibitor or tamoxifen" ("HER2-Positive Breast Cancer") . Trastuzumab is also a type of immune therapy that is known as a monoclonal antibody. "A monoclonal antibody is a man-made version of an immune system protein that fits like a lock and key with one certain protein" ("Trastuzumab") . Once Trastuzumab attaches to the cells with excessive amounts of HER2 protein, it brings in other immune cells to help kill them. This specific drug is given by infusion in a vein. The first dose of Trastuzumab is usually given over ninety minutes, and the next over thirty minutes. The treatment usually lasts for a total of one year. With the first treatment, it is possible that the drug may cause an allergic reaction, but it is not as common after the very first treatment. Common side effects may include fever, headache, chills, nausea, vomiting, and shortness of breath. Other rare, serious side effects include damage to the heart if used with chemotherapy drugs called anthracyclines and lung disease. It is important to note that

Trastuzumab may affect your immune system, especially if used with chemotherapy. It can lower both white blood cell counts and red blood cell counts. It is recommended that patients do not get any immunizations during or directly after treatment with this drug, because it could make vaccinations ineffective, or lead to serious infections ("Trastuzumab") . This drug will more than likely harm a fetus, so it is not to be taken while pregnant; it is advised to take birth control while on this drug if there is any chance of pregnancy. Trastuzumab was FDA approved in 1998.

Lapatinib, also known as Tykerb, may be effective for HER2-positive cancers that do not respond to Trastuzumab. Lapatinib is a type of targeted therapy known as a tyrosine kinase inhibitor. "Tyrosine kinases are proteins at the surface of a cell that signal its control center to divide and grow. Lapatinib blocks the signals from the HER2 tyrosine kinase" ("Lapatinib") . Lapatinib can be used in combination with the chemotherapy drug Capecitabine (Xeloda) and the aromatase inhibitor Letrozole (Femara) ("HER2-Positive Breast Cancer) . It is important for patients taking this drug to discuss with their doctors what other medications they are taking along with Lapatinib. Certain drugs can cause Lapatinib to build up in the body, raising the risk of serious side effects. A few of these drugs include the antidepressant Nefazodone (Serzone) and the antibiotics Erythromycin (EES), Clarithromycin (Biaxin), and Telithromycin (Ketek) ("Lapatinib") . Other drugs may lower the levels of Lapatinib in the blood and make it less effective. Some of these drugs include anti-seizure drugs Tegretol, Luminal, and Dilantin, along with the steroid drug Decadron, and TB drugs such as Rifadin, Priftin, and Mycobutin ("Lapatinib") . Lapatinib is taken in pill form and is taken five to six times a day to begin with. The dosage will change later on depending on what side effects are present. Like Trastuzumab, this drug may rarely lower the patient's red blood cell count, which can cause anemia. Common

side effects include diarrhea, rash, and Hand-Foot Syndrome, which includes red, swollen, numb, or painful hands and feet. Other rare, serious side effects may include effects on heart rhythm or function, anemia, liver problems, or possibly even death due to liver failure, diarrhea, or other causes ("Lapatinib") . Lapatinib was FDA approved in 2007.

Pertuzumab, also known as Perjeta, is another type of targeted immunotherapy known as a monoclonal antibody. It is designed to seek out and lock onto HER2 proteins. Like Trastuzumab, it attracts immune cells to help kill the cancer cells. Pertuzumab may be used in combination with Trastuzumab ("Understanding HER2-Positive Breast Cancer") . Unlike with Lapatinib, it is not yet clear if Pertuzumab has negative reactions in combination with other drugs. "Pertuzumab could possibly interact with other drugs known to damage the heart, such as certain chemotherapy drugs called anthracyclines" ("Pertuzumab") . This drug is given by infusion in a vein. It can be given along with other cancer drugs once every three weeks. Common side effects include diarrhea, nausea, hair loss, and feeling tired or weak. Other rare, serious side effects include serious allergic reactions, damage to the heart, and a lowered red blood cell count ("Pertuzumab") . Pertuzumab was FDA approved in 2012.

"Another area of interest is the phosphatidylinositol-13 kinase (P13K) inhibitor. Lab research has demonstrated that HER2 signals through the P13K pathway. In addition, about one-quarter of HER2-positive tumors contain a mutation, or error, in the P13K gene" (Fernandez, "How Far We've Come") . People with tumors that have this P13K mutation seem to be more resistant to standard therapies. Different inhibitors are currently being tested to reverse those mutations (Fernandez, "How Far We've Come") . In addition to the P13K gene, studies have shown that about seventy-five percent of HER2 type tumors contain p53 mutations ("Emerging Areas") . Perhaps it may be beneficial to closely study a patient's genes to see what specific

genes have mutated. This may help doctors determine which form of treatment will be most effective for their patient.

It is also important to note that it is possible for cancer cells to lose or gain HER2 receptors and other hormone receptors. This means that at any time, a patient may have to switch their treatment to something more effective. It is very important for doctors to periodically test for hormone receptors, because if their patient is positive for hormone receptors, hormone therapy may be the most effective treatment, while if their patient is negative for hormone receptors, targeted therapies may be more effective ("HER2 Status") .

Chemotherapy

Chemotherapy, unlike targeted therapies, is a form of systemic therapy, meaning it affects the entire body by traveling through the bloodstream. Chemotherapy treatment uses drugs to weaken and destroy tumor cells in the body, not just at the original cancer site, but also other cancer cells that may have spread to other parts of the body, otherwise known as metastatic cancer ("Chemotherapy") . Chemotherapy is used to treat " early-stage invasive breast cancer to get rid of any cancer cells that may be left behind after surgery and to reduce the risk of the cancer coming back" ("Chemotherapy") . It is also used to treat "advanced-stage breast cancer to destroy or damage the cancer cells as much as possible. In some cases, chemotherapy is given before surgery to shrink the cancer" ("Chemotherapy") . This is referred to as neoadjuvant chemotherapy. When chemotherapy is given after surgery, it is termed adjuvant chemotherapy because it is "given in addition to surgery, which is considered the primary treatment" ("How Chemo Works") . Usually different chemotherapy medicines are given in combination, "which means a patient receives two or three different medicines at the same time. These combinations

are known as chemotherapy regimens. In early-stage breast cancer, standard chemotherapy regimens lower the risk of cancer coming back. Early stage breast cancer generally means cancer that is classified as stage 0, stage I, stages IIA or IIB, and some stage III. In advanced breast cancer, chemotherapy regimens make the cancer shrink or disappear in about thirty to sixty percent of people treated. Advanced-stage breast cancer generally means cancer that is classified as some stage III, and stage IV" ("How Chemo Works") .

There are several different chemotherapy drugs used for breast cancer treatment. A couple of popular groups of chemotherapy medicines include Anthracyclines and Taxanes. "Anthracyclines are chemically similar to an antibiotic. They damage the genetic material of cancer cells, which makes the cells die. Adriamycin, Ellence, and daunorubicin are all anthracyclines" ("Chemotherapy Medicines") . "Taxanes interfere with the way cancer cells divide. Taxol, Taxotere, and Abraxane are all Taxanes" ("Chemotherapy Medicines") . Most chemotherapy regimens include a medicine from one or both of these groups. When deciding on a chemotherapy regimen, a doctor will consider the characteristics of the cancer and the patient's menopausal status and general health ("Choosing a Chemotherapy Combination") .

Chemotherapy side effects tend to be more severe than other forms of cancer treatments. Chemotherapy can unintentionally harm other types of rapidly diving cells, including cells in hair follicles, nails, the mouth, digestive tract, and bone marrow, thus leading to more severe side effect compared to other treatments.

Some of the common side effects include anemia, hair and nail changes, infection, neuropathy, weight changes, nausea, and vomiting. Other less common, but more serious side effects may include osteoporosis, heart problems, and vision and eye problems ("Managing Chemotherapy Side Effects") .

Radiation Therapy

"Radiation therapy uses a special kind of high-energy beam to damage cancer cells. These high-energy beams, which are invisible to the human eye, damage a cell's DNA, the material that cells use to divide. Over time, the radiation damages cells that are in the path of its beam, including normal cells as well as cancer cells ("How Radiation Works") . However, radiation affects tumor cells more so than normal cells. "Cancer cells are very busy growing and multiplying, which are two activities that can be slowed or stopped by radiation damage. And because cancer cells are less organized than healthy cells, it is harder for them to repair the damage done by radiation. So, cancer cells are more easily destroyed by radiation, while healthy, normal cells are better able to repair themselves and survive the treatment" ("How Radiation Works") . Radiation is usually used to kill cancer cells that may still exist after having surgery to remove the cancer; however, radiation may be given after other forms of treatment such as chemotherapy, targeted therapy, or hormonal therapy.

There a two main ways to deliver radiation to the cancerous tissues. These include "a machine called a linear accelerator that delivers radiation from outside the body, and pellets, or seeds, of material that give off radiation beams from inside the body" ("How Radiation Works") . Usually once an area has received full radiation treatment, that same area cannot be given another full radiation treatment, due to health risks. Current ongoing studies show that hyperthermia used in combination with radiation therapy may make some cancer cells more sensitive to radiation. Hyperthermia, a form of thermotherapy, "uses an energy source such as ultrasound or microwave to heat cancer cells to high temperatures, up to one hundred thirteen degrees Fahrenheit" ("How Radiation Works") .

Common side effect include armpit discomfort, chest pain, fatigue, heart problems, lowered white blood cell counts, lung problems, and perhaps the most common, skin reactions ("Managing Other Side Effects of Radiation") . A common misconception is that radiation therapy is painful. However, "most patients have no sensation of radiation when the machine is delivering the daily treatment. A few patients report a slight warming or tingling sensation in the area while the radiation machine is on" ("Myths About Radiation Therapy") . The skin in the area being treated may become uncomfortable gradually over time due to it becoming dry, sore, itchy, or burning.

Prognosis

When determining a patient's prognosis, a doctor will consider many factors. These factors include the size of the breast cancer, the stage of the breast cancer, the type of breast cancer, the hormone-receptor status of the cancer, HER2 status, the rate of cell growth, recurrence, age, menopausal status, and the patient's general health ("What Does Prognosis Mean") .

Breast Cancer Stage	5-Year Survival Rate for Women
0	93%
I	88%
IIA	81%
IIB	74%
IIIA	67%
IIIB	41%
IIIC	49%
IV	15%

Table 1: 5-Year Survival Rate for Women

Breast Cancer Stage	5-Year Relative Survival Rate for Men
0	100%
I	96%
II	84%
III	52%
IV	24%

Table 2: 5-Year Survival Rate for Men

According to American Cancer Society, the 5-year survival rates for women and men are shown above in Tables 1 and 2. Overall, the survival rates for men are higher than the survival rates for women.

Conclusion

Research has shown that different treatments in combination with one another have proven effective for treating breast cancers. Although chemotherapy and radiation appear to be more harmful on the body than say hormonal therapies and targeted therapies, perhaps using them in combination with one another is indeed a step toward the right path. It is highly unlikely that there will be a single cure for all cancers, let alone breast cancers in general. Perhaps if further research could be done over the different types of gene mutations that occur in cancers, we may be able to find a trend that could lead to us discovering a so called "magic bullet" that will provide clues to how we can effectively treat, and possibly cure, cancers found in multiple places throughout the body. It seems as though focusing on the specific genes that are mutated may be the key to determining which form of treatment is most effective. If we are able to determine which genes are being mutated in each patient, we may be able to create an effective magic bullet to target those specific cancerous cells and genes. Better yet, we may be able to find a more effective way to deliver drugs to the site of the cancer and have it kill only the cancer cells, not the surrounding healthy cells as well. Recent research on green tea and its antioxidant epigallocatechin gallate (EGCG) suggests that scientists may have found a new and effective drug delivery system, which kills cancer cells more efficiently. Researchers found that when drugs, such as Herceptin, were encapsulated in this green tea-based "missile", the protein drugs were delivered more effectively to the cancer cells, and it dramatically reduced tumor growth

compared with the drug alone (“Green Tea”) . Small discoveries like this may very well lead to us discovering our oh-so desired magic bullet to help us discover cures for cancer.

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