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Surviving Cancer is not the end of the story: Effects of Chemotherapy on Heart Function.

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Abstract description: Cancer is a disease that has killed millions and cost trillions. It is a tragic disease, and while the treatment used may help fight cancer, potential long-lasting damage is inflicted onto the heart. Chemotherapies are widespread drugs used to treat any and all kinds of cancer. There are many different classes including, but not limited to, the anthracyclines, taxanes, monoclonal antibodies, alkylating agents, tyrosine kinases, and antiestrogens. For patients with breast cancer, there are about 69 different chemotherapies approved for treatment, and they are all from a variety of different classes. However, most of the classes of chemotherapies are associated with some kind of cardiotoxicity. The anthracyclines are associated with Type 1 cardiotoxicity, meaning that the damage induced on the heart is irreversible and often leads to heart failure. The monoclonal antibodies are associated with Type 2 cardiotoxicity, meaning that the damage induced is typically reversible and that it is not dose dependent. This kind of damage is typically repaired upon completion of chemotherapy treatment and possibly going on heart medications. With that being said, depending on the specific chemotherapy used, it can be given in a situation where a type 2 chemotherapy induces type 1 effects, such that a monoclonal antibody is given with or too soon after anthracycline treatment. The goal of this thesis is to examine one of each of the above classes of

chemotherapeutic drugs. The mechanism of action and the effects on the heart are discussed in detail.

Keywords and phrases: chemotherapy, cardiotoxicity, anthracyclines, dexrazoxane, taxanes, monoclonal antibodies, alkylating agents, tyrosine kinases, antiestrogens

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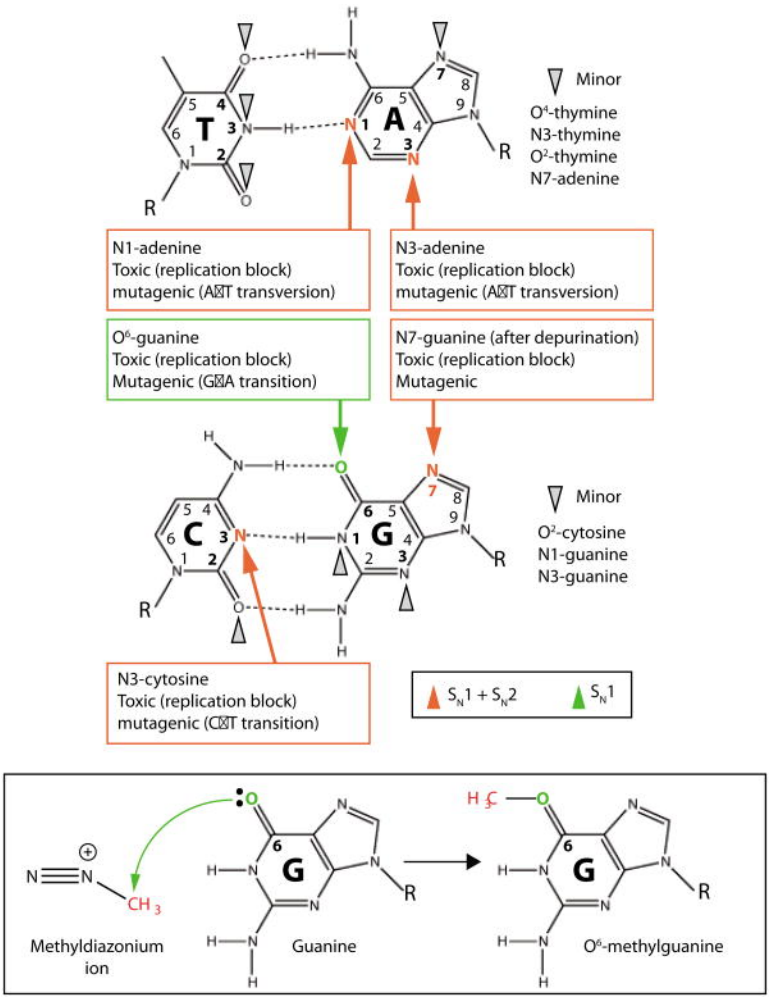
DNA bases alkylation



(Fu, Calvo, & Samson, 2013).

Figure 2

Cyclophosphamide Metabolism

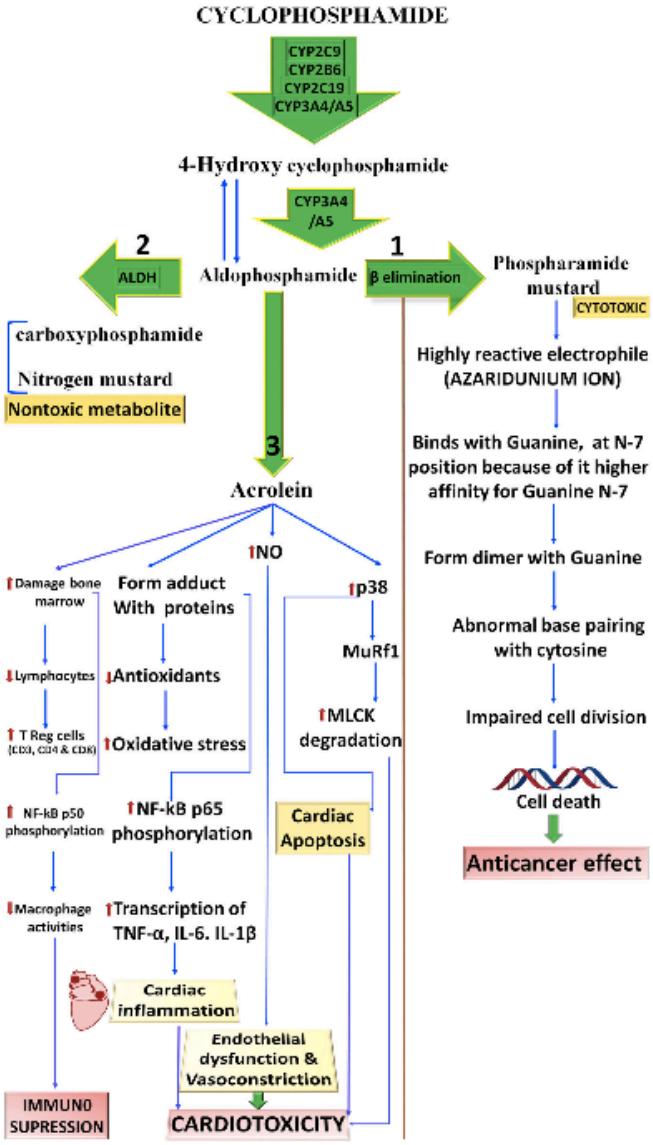


Fig. 1. Showing metabolism of Cyclophosphamide (CP). CP undergoes hepatic metabolism and forms 4-hydroxy cyclophosphamide (4-HCY) which further metabolizes into aldophosphamide. Aldophosphamide produces phosphoramide mustard via β-elimination which show anti-cancer activity. Aldophosphamide further metabolizes into non-toxic metabolites like carboxyphospamide and nitrogen mustard along with toxic compound acrolein which is mainly responsible for CP induced toxicities.

(Iqubal, et al., 2019).

Tables

Table 1

Chemotherapy Drug Details

Chemotherapy	Side Effects	Class	Method of Dosage	How often?
Lapatinib (Tykerb)	Liver damage, shortness of breath, heartburn, fast or irregular heart beat	Kinase Inhibitors	Oral	1/day
Trastuzumab	Heartburn, Short of Air, Fast/irregular heart beat	Monoclonal antibodies	Liquid IV	1/week
Cyclophosphamide	Difficulty breathing, SOB, chest pain	Alkylating agents	Injected Powder	Depends
Docetaxel	Extreme tiredness, stomach pain	Taxanes	Liquid IV	3 weeks
Doxorubicin Hydrochloride	Heart problems	Anthracyclines	Liquid IV	1x every 21-28 days
Tamoxifen Citrate	Coughing up blood, SOB	Antiestrogens	Oral	Twice a day

Acknowledgement

I would like to thank my mentor, Dr. Lisa Middleton, for helping me through this process and for all of the advice given about research and my career. I would also like to give a huge thanks to my family for supporting me throughout school and life. They have been the biggest blessings and have allowed me to grow not only as a student but also as a person. My parents and sister have made so many sacrifices for me, and I am eternally grateful.

According to the World Health Organization, cancer killed 9.6 million people worldwide in 2018, and in 2010, the total cost of cancer was around 1.16 trillion dollars (2018). Cancer is a disease that is characterized by cells continually dividing in the body without control. Chemotherapies are drugs used to disrupt this process and restart the body's normal process of creating cells as needed and killing those cells that are damaged and/or are old. The primary objective of chemotherapy is to "impair mitotic and metabolic process of cancer cells"; however, these drugs are so potent, that they do not only destroy those cells, but healthy cells, as well (Angsutararux, Luanpitpong, and Issaragrisil, 2015). Chemotherapies are an essential part of the treatment for cancer, and although it saves many people from the horrible fate of cancer, it has its known side effects that can cause many long-standing issues alone.

Within the last 50 years, there have been many studies performed on those who have had chemotherapies in their past. It is now known that although these

drugs are wonderful for the treatment of cancer, it is detrimental to heart function. According to the National Cancer Institute, the toxic effects on the heart, known as cardiotoxicity, were first identified in the 1960s. The different types of cardiotoxicity identified were acute, subacute, and chronic (Mihalcea, Florescu, & Vinereanu, 2017). Acute cardiotoxicity is toxicity that occurs within 2 weeks of starting the treatment while subacute cardiotoxicity occurs after 2 weeks of starting the treatment (Mihalcea, Florescu, & Vinereanu, 2017). Chronic cardiotoxicity occurs either within 1 year or after 1 year, which typically leads to heart failure and death (Mihalcea, Florescu, & Vinereanu, 2017).

Depending on the type of chemotherapy and the duration of treatment, the effects on the heart are widely varied. For example, some classes of chemotherapy may cause a temporary irregular heartbeat whereas other therapies may lead to myocyte vacuole degeneration, which is injury to the cardiac muscle cells. (Angsutararux, Luanpitpong, and Issaragrisil, 2015). Because it is known that chemotherapies do have an effect on the heart, there have been multiple studies performed to determine how to treat and/or prevent chemotherapy-induced cardiotoxicity. Those who fight the long battle of cancer deserve a better treatment option that is not only effective in fighting cancer, but also comes without the lifelong and potentially irreversible damage to the heart.

Cancer is a disease, and like any other disease, there are multiple drugs that can attempt to rid the body of the destructive cells. There are different classes of chemotherapies ranging from the anthracyclines to the monoclonal antibodies. Because there are so many different classes and specific drugs approved for the use

of all cancers, only those that are approved for the use of breast cancer will be considered. According to the World Health Organization, breast cancer tied with lung cancer for the number of cases in 2018, which was 2.09 million each worldwide; moreover, breast cancer is also in the top 5 for cancer deaths at 627,000 deaths in the world (2018). According to the National Cancer Institute, there are about 69 chemotherapies that have been approved to treat those with breast cancer, and many of those are in different chemotherapy classes, meaning that the drugs have different mechanisms of actions and levels of potency (2019). There are many different types of breast cancer, with one of those being HER2-positive breast cancer. This kind of breast cancer has a protein known as human epidermal growth factor receptor 2 (HER2) that fosters the growth of cancer cells; furthermore, these kinds of cancers are inclined to be more aggressive than any other type of breast cancer (Mayo Clinic, 2020). Some other types of breast cancer include angiosarcomas, which is less than 1% of breast cancers; inflammatory breast cancer, which is between 1-5% of breast cancers; and triple-negative breast cancer, which is about 15% of breast cancers (American Cancer Society, 2019). The chemotherapy classes that will be discussed include anthracyclines, monoclonal antibodies, taxanes, alkylating agents, and kinase inhibitors. For each of the classes of common chemotherapies, the mechanism of action in the body, and its toxic effects on the heart will be discussed.

When discussing cardiotoxicity, the classes and individual drugs are divided into Type I and Type II chemotherapies. Type I chemotherapies are those drugs that predominantly cause irreversible damage due to cell loss resulting in

pathophysiology, or injury, of the heart; however, Type II chemotherapies are those drugs that predominantly cause reversible damage due to alterations in the mitochondria and proteins in the heart (Curigliano, et al., 2012). With Type II chemotherapies, often patients can return to normal cardiovascular function with time; whereas, Type I chemotherapies can induce progressive cardiovascular disease (Curigliano, et al., 2012). These classifications are based on what generally occurs with the use of the specific chemotherapy. However, there are exceptions where a drug may be classified as Type II chemotherapy but when presented in the right circumstances can trigger Type I-like effects. The severity of the cardiotoxicity is also determined by the route of administration of the chemotherapy, the dosage course, and the duration of the treatment (Angsutararux, Luanpitpong, and Issaragrisil, 2015). As seen in Table 1, all of the drugs in the classes discussed in this paper can cause some serious side effects; however, not all of them are associated with the cardiotoxic effects in which some of the classes are known. The differences in these chemotherapies (their mechanisms and effects) and their classes will be examined in the entirety of this paper.

Anthracyclines

The class of chemotherapies known as the anthracyclines is very widely used for many different malignancies, but is most often used to treat breast cancer. Doxorubicin is a first-line treatment and is used to treat 32% of those with breast cancer (McGowan et al., 2017). However, the anthracyclines as a whole are considered to be a Type I chemotherapy and are considered to give rise to heart

defects that are more common and detrimental than other chemotherapy classes (Angsutararux, Luanpitpong, and Issaragrisil, 2015). Because of the wide range of effects that the anthracyclines can impose, the effects are divided into acute and chronic. Acute effects are those that occur directly after or during the course of the treatment and are typically reversible; whereas, the chronic effects are those that can occur years after the treatment and are frequently more detrimental to the heart (Angsutararux, Luanpitpong, and Issaragrisil, 2015). Risk factors in developing cardiotoxicity following anthracycline treatment include age (those younger than 18 and older than 65 are at a greater risk), pre-existing conditions, and renal failure; hence, those that have a greater number of risk factors, have an even greater chance of developing congestive heart failure following treatment (Zamorano, et al., 2016).

The anthracyclines are drugs that target the Topoisomerase-alpha enzyme in cancer cells that exhibit an extreme division cycle (Tadic, Cuspidi, Hering, Venneri, & Danylenko, 2017). In a healthy cell, the topoisomerases produce protective effects on the cell. Topoisomerase-2β is found largely in cardiomyocytes, cells making up the heart muscle, thus causing damage to the heart when harmed. However, doxorubicin binds to the Topoisomerase-2β enzyme and lowers its ability to protect against DNA replication normally (Swiger, Singh, & Lenihan 2017). Topoisomerase-α is structurally identical to Topoisomerase-2β, so anthracyclines affect both leading to anthracycline-induced cardiomyopathy (Tadic, Cuspidi, Vasic, & Kerkhof, 2018). This isoenzyme, Topoisomerase-α, binds to doxorubicin and triggers mitochondrial dysfunction (McGowan et al., 2017).

During mitochondrial DNA recombination, Topoisomerase-2β controls the chromatin relaxation and condension, while also promoting the rearrangement of genes (Goffart, Hangas, & Pohjoismäki, 2019). The mitochondrial DNA in mammals is usually in the shape of a circle, but can be relaxed or coiled tightly; nevertheless, the mitochondrial DNA in cardiomyocytes are much more complex in that they form networks with other mitochondria (Goffart, Hangas, & Pohjoismäki, 2019). Because of this, Topoisomerase-2β, as well as other subunits of topoisomerase, is needed to relax the coiling during the DNA replication and transcription (Goffart, Hangas, & Pohjoismäki, 2019). Anthracyclines inhibit Topoisomerase-2β causing the DNA to stay coiled tightly; similarly, there has also been evidence of changes in the structure of mitochondrial DNA attributable to the breaks in the double strands of DNA that presents with topoisomerase poisoning (Goffart, Hangas, & Pohjoismäki, 2019).

The mitochondria in cardiomyocytes generate reactive oxygen species through the electron transport chain (Siasos et al., 2018). Doxorubicin-induced cardiotoxicity may be caused by a multitude of effects including damage to the mitochondria, apoptosis, and an increase in oxidative stress (Potočnik, et al., 2017). Anthracyclines in general are known to invoke intracellular damage due to the production of hydroxyl radicals that are tremendously toxic to the body; correspondingly, these are made by the production of highly reactive oxygen species (oxygen species reacting with iron), which are exacerbated with anthracycline treatment (Tadic, Cuspidi, Vasic, & Kerkhof, 2018). This oxygen species leads to an increase in apoptosis and deterioration. Anthracyclines, in general, evoke harm on

the mitochondria and Topoisomerase-2β, which leads to a plethora of other damage and can ultimately lead to heart failure.

The peroxisome proliferator-activated receptor (PPAR) regulates oxidative metabolism, which also occurs in the mitochondria (McGowan et al., 2017). This receptor is activated by a ligand binding to the active site, causing the receptor to undergo a conformational change that ultimately regulates gene transcription (Lee & Kim, 2015). The receptor is found in 3 different subtypes in the body: alpha, gamma, and beta (Tyagi, et al., 2011). The alpha, α, subunit allows for energy to be generated for the heart muscle and other areas of the body in playing a crucial role in the breakdown of fatty acid molecules in the liver (Tyagi, et al., 2011). The gamma, γ, subunit acts as a receptor and regulates fatty acid storage (Tyagi, et al., 2011). A study using PPAR-gamma knockout mice, which "exhibit progressive cardiac fibrosis with abnormal mitochondria and myofibrils," has demonstrated that this isoform of PPAR is crucial in the protection of cardiomyocytes (Lee & Kim, 2015). Lastly, the beta, β, subunit, promotes fatty acid metabolism; however, it has also been demonstrated that the ligand could potentially inhibit cardiac hypertrophy (Tyagi, et al., 2011). One study of cardiomyocytes taken from mice showed that doxorubicin significantly decreased the amount of the PPAR-beta receptor. As PPAR is protective, cells that exhibit a decrease in receptor number will lose the ability to effectively protect against cardiac hypertrophy as the cells have become desensitized (Chen, Chen, & Cheng, 2013). Having too much or too little of the PPAR, however, could potentially foster cardiomyopathy or further myocardial damage (Lee & Kim, 2015).

Anthracyclines are transformed from a quinone form to a semiquinone form (one electron reduction form) by enzymes in the mitochondria (Angsutararux, Luanpitpong, & Issaragrisil, 2015). Furthermore, the formation of the semiquinone form of the anthracycline (in the body) reacts promptly when in contact with oxygen; likewise, when it reacts with the oxygen, a superoxide anion is formed along with a hydrogen peroxide, which then leads to an increase in the number of reactive oxygen species (Edwardson. et al., 2015). As discussed previously, an increase in the number of reactive oxygen species would increase the rate of apoptosis in cells (Siasos et al., 2018). This process has been discovered to occur in the mitochondria, cytoplasm, and sarcoplasmic reticulum and create toxic aldehydes that escape the cells (Edwardson, et al., 2015). For the heart, however, the semiquinone form of the anthracycline is more associated with the dysfunction that the form induces to the mitochondria; moreover, the heart needs adenosine triphosphate (ATP) to pump blood throughout the body and any damage to the mitochondria would impair that process (Edwardson, et al., 2015). According to Edwardson, D.W., cardiomyocytes acquire about 90% of their ATP from the mitochondria (2015). The formation of the semiquinone form of an anthracycline inducing damage on the mitochondria in cardiomyocytes reduces the ATP that is formed and ultimately impairs the heart's ability to pump blood throughout the body.

Anthracyclines can also go through the reduction of two electrons when in the body, and the product, secondary alcohol metabolites, have been suggested to be a potential factor in cardiotoxicity induced by anthracyclines (Edwardson, et al., 2015). However, the products (hydroxylated anthracyclines) only inflict a greater

amount of cardiotoxicity than the parent compounds due to their ability to collect in the tissue of the heart; moreover, the products collect a significant amount more in the heart than anywhere else in the body (Edwardson, et al., 2015). The reasoning behind why the products accumulate more in the heart is unknown (Edwardson, et al., 2015). However, the consequence of hydroxylated anthracyclines building up in the heart is the onset of cardiomyopathy; furthermore, this could occur at any time between the beginning of the treatment to months later (Edwardson, et al., 2015).

Doxorubicin is an especially prevalent and effective anthracycline that is used to treat a variety of different cancers. However, the drug is known for its extremely damaging effects on the heart. According to Angsutararux, Luanpitpong, and Issaragrisil, the cumulative amount of doxorubicin that is given is crucial to the likelihood of succumbing to heart failure following treatment, as exceeding $550 mg/m^2$ considerably increases the chances of ending up with congestive heart failure from 4% to 18% (2015). Similarly, the risk jumps up to a 48% chance when receiving $700 mg/m^2$ (Zamorano, et al., 2016).

Moreover, one study demonstrated that the use of doxorubicin over a 6-week time frame almost completely rids the body of cardiac-resident stem and progenitor cells in the myocardium, both of which are stem cells that commit to becoming cardiomyocytes (Madonna, et al., 2017). Doxorubicin and other anthracyclines have harmful effects on both the cardiomyocytes and the stem cells that commit to becoming cardiomyocytes. Without these stem cells, the damage becomes irreversible and no new cells can be produced.

Monoclonal Antibodies

Monoclonal antibodies are another class of chemotherapies that is widely used in the treatment of many cancers, including breast cancer. These immune system proteins are made in the lab to act like the body's antibodies and acknowledge specific targets (National Cancer Institute, 2019). The proteins can only bind to one substance each, with one of those being cancer cells (National Cancer Institute, 2019). Monoclonal antibodies can be used alone or with other chemotherapeutic agents in order to carry substances directly to the cancer cells (National Cancer Institute, 2019). Some monoclonal antibodies target the immune system, turning it against the cancer cells, while also binding to the cancer cells in order to help the immune system kill the cancer cells (National Cancer Institute, 2019). Monoclonal antibodies were not originally meant for chronic therapy, but later on more human-like monoclonal antibodies were developed (Shepard, et al., 2017).

Monoclonal antibodies are Type 2 chemotherapies because the effects on the heart are not dose-dependent and the damage they can cause to the heart is normally reversible (Tadic, Cuspidi, Hering, Venneri, & Danylenko, 2017). However, monoclonal antibodies can contribute to the progression of a tumor similar to other immunosuppressant drugs and cause cardiotoxicity (Singh, et al., 2018). The first monoclonal antibody was approved by the FDA for cancer treatment (specifically lowgrade B cell lymphoma) in 1997; likewise, there are now over 60 different monoclonal antibodies that the FDA has approved (Singh, et al., 2018).

A common monoclonal antibody used in the treatment of breast cancer is trastuzumab (Tadic, Cuspidi, Vasic, & Kerkhof, 2018). The tyrosine-protein kinase expressed on cancer cells is inhibited by trastuzumab; however, cardiomyocytes express the same kinase and when inhibited, dilated cardiomyopathy is evoked, which is blood pumping less effectively through the heart due to the expansion, or dilation, of the left ventricle (Tadic, Cuspidi, Vasic, & Kerkhof, 2018). The human epidermal growth factor receptor type 2 that trastuzumab inhibits, regulates growth and survival of cardiomyocytes and other cells (Higgins, O'Halloran, & Chang, 2015). The chemotherapy has also been linked to the inhibition of the neuregulin-1, which normally activates the human epidermal growth factor receptor type 2 on cardiomyocytes as a protective mechanism (Nicolazzi, et al., 2018). This inhibition, though, causes the inability of the cardiomyocyte to maintain sarcomeres (allows the lower chambers of the heart muscle to contract in unison and the upper chambers of the heart to contract in unison) and subproducts of ATP formation. Moreover, this leads to oxidative stress and the upregulation of angiotensin II, which prevents neuregulin-1 from binding to other receptors to make up for the blockage of the human epidermal growth factor receptor type 2 and also induces apoptosis (Nicolazzi, et al., 2018). This, in turn, leads to greater oxidative stress. Trastuzumab blocks all of the possible ways for the cardiomyocytes to repair themselves and regulate their survival, therefore, damaging the heart (but not to the point of no return). After discontinuing treatment, the heart will be able to work back up to regulating the cardiomyocytes and the sarcomeres and making any repairs that will need to be made to the heart.

Because this kinase receptor regulates survival of the cardiomyocytes, when it is inhibited, the cardiomyocytes' ability to repair itself and respond to stress and injury are also compromised (Higgins, O'Halloran, & Chang, 2015). According to Higgins, O'Halloran, and Chang, after discontinuing the chemotherapy, the patients in a study all recovered, with 16% being spontaneous and 84% being with heart failure treatment (2015). With that being said, if trastuzumab is given with anthracycline treatment or given too soon after anthracycline treatment, the damage can become permanent, making it, in this instance, a type 1 chemotherapy that can lead to the development of congestive heart failure (Higgins, O'Halloran, & Chang, 2015). Because trastuzumab prevents the heart from repairing itself, the cardiomyocytes will not be able to repair some of the damage induced by the anthracyclines if it is introduced too soon after anthracycline treatment. The damage induced by the anthracyclines will then be built on by the "reversible" damage of trastuzumab; however, with damage already being done, the trastuzumab damage will become permanent. Other factors that will put patients at an increased risk of cardiotoxicity include smoking, diabetes, hypertension, age (older than 49 years old), a decreased left ventricular ejection fraction, or any preexisting cardiac diseases (Higgins, O'Halloran, & Chang, 2015).

In patients treated only with trastuzumab, and not anthracyclines before or during trastuzumab treatment, the incident of cardiomyopathy is much lower; furthermore, there is no difference in the thickness of the right and left ventricle walls in a study on mice who were only treated with trastuzumab (Tadic, Cuspidi, Hering, Venneri, & Danylenko, 2017). This suggests that treatment with

trastuzumab, when used to treat cancer, prevents the changes that anthracyclines typically induce and has some cardioprotective effects while also fighting the cancer cells; however, it can cause some reversible damage of its own. Trastuzumab-induced left-ventricular contractile dysfunction occurs at a rate of around 3% when given without other chemotherapies (most common); whereas, the risk of heart failure to patients treated with trastuzumab according to a study of 11,000 patients was 2.5% (Higgins, O'Halloran, & Chang, 2015). Trastuzumab in breast cancer has led to a 50% decrease in the cancer returning and has also improved the survival rate to 33% of those treated with trastuzumab (Curigliano, et al., 2012). In an 11-year study of patients treated with trastuzumab after another chemotherapy (anthracyclines and/or taxanes) in the treatment of breast cancer, the observation group had 63% of patients with 10 years free of disease; however, there was 69% of patients with 10-year survival and no diseases for both the group treated with 1 year of trastuzumab and 2 years of trastuzumab (Cameron, Piccart-Gebhart, & Gelber, 2017). Therefore, there is a significant improvement in the disease outcome.

However, in one study, elevation of the right ventricle filling pressure signified a decrease in the diastolic function of the right ventricle of the heart (Tadic, Cuspidi, Hering, Venneri, & Danylenko, 2017). In another study of 9 female breast cancer patients, it was discovered that after 6 months of trastuzumab therapy, the circumferential strain on the right ventricle decreased, but the systolic function of the right ventricle was normal (Tadic, Cuspidi, Hering, Venneri, & Danylenko, 2017). Circumferential strain is a measure of the reduction of the diameter of the ventricles, and thus, a measure of cardiac dysfunction (Støylen, 2018). Overall,

trastuzumab is a safer treatment option for cancers because the damage it induces is typically reversible, unless it used in combination with anthracyclines, and it has demonstrated an increase in the survival rate of those with breast cancer.

Taxanes

The taxanes, discovered in the 1960s, are a chemotherapeutic class that is most often used in the treatment of breast cancer, as it is one of the most effective in treating the cancer (Gradishar, 2012). It was first used for humans in the 1990s, specifically for metastatic breast cancer, because in doing clinical trials, there was hope that it would have improved outcomes in both early and late stage cancer (Gradishar, 2012). Compared to other chemotherapy regimens, the patient survival rate when treated with taxanes versus other chemotherapeutic agents is higher; furthermore, the survival rate of those with metastatic breast cancer between 1991 and 1995 was only 34%, but between 1997 and 2001, the survival rate had increased to 45% at 2 years (Ho & Mackey, 2014). As of 2016, all of the taxane drugs are FDA approved to be administered intravenously (Ojima, Lichtenthal, Lee, Wang, & Wang, 2016).

The taxane chemotherapeutic class promotes both bradyarrhythmias and tachyarrhythmias, which both can lead to heart failure (Lage, et al., 2019). The cardiotoxic risks of taking taxanes are not quite known (Zamorano, et al., 2016). It is known, however, that the taxanes can activate apoptotic pathways (Lage, et al., 2019). Furthermore, taxanes prevent the mitotic spindle from going through depolymerization by stabilizing the microtubules β-tubulin subunit (Lage, et al.,

2019). This causes cell cycle arrest in both the G2 and Mitosis phases of the cell cycle, which then causes cell death (Gradishar, 2012). The cell is not able to go through mitosis because the microtubules are not able to pull the chromosomes to the opposite side of the cell to go through with cytokinesis, so the cell activates apoptosis.

Docetaxel is a derivative of paclitaxel (the original taxane discovered in the 1960s) that is more potent (Gradishar, 2012). It was discovered in the 1980s, and received Food and Drug Administration (FDA) approval in 1996 for the treatment of breast cancer that has returned for at least the 2nd time (Gradishar, 2012). Docetaxel is a chemotherapeutic agent that is used in the treatment of many cancers, including breast cancer and lung cancer. Some toxicities induced by docetaxel include edema (swelling) and shortness of breath (Ojima, et al., 2016). The chemotherapy often comes with acute infusion reactions, which means that the symptoms occur within minutes or hours of receiving the dose of docetaxel; moreover, these symptoms include fever, hypoxia (low oxygen in the blood), dyspnea (difficulty breathing), cardiorespiratory arrest and anaphylaxis (Ho & Mackey, 2014).

Docetaxel treatment increases the activity of NADPH oxidases, which is the source of most of our oxygen production; furthermore, this results in an increase in reactive oxygen species (Lage, et al., 2019). An increase in the reactive oxygen species decreases the amount of ATP produced, and then increases the rate of apoptosis, which ultimately leads to damage of the heart (Siasos et al., 2018).

Heart failure induced by the use of paclitaxel and docetaxel in patients is anywhere from 2.3-8% of patients (Min & Wierzbicki, 2017). LVEF, left ventricular

ejection fraction, reductions of at least 15% have presented in 6-8% of patients (Madeddu, et al., 2016). There have also been cases of myocardial ischemia (blocked blood flow to the heart) in those treated with either paclitaxel or docetaxel (Min & Wierzbicki, 2017). Docetaxel stabilizes microtubules, and may therefore, cause contractile dysfunction; furthermore, left ventricular diastolic dysfunction has been determined to be induced by docetaxel (Shimoyama, et al., 2001). One of the known causes of congestive heart failure is diastolic dysfunction (Shimoyama, et al., 2001). If docetaxel induces left ventricular diastolic dysfunction, the risk of developing congestive heart failure is going to increase with the use of docetaxel.

A 62-year-old Hispanic man was diagnosed with metastatic prostate cancer and was being treated with docetaxel (Huq, Balvanz, & Mambourg, 2018). Within 15 minutes of the 2nd cycle of chemotherapy being infused, the patient developed a stable, but chronic, atrial fibrillation (Huq, Balvanz, & Mambourg, 2018). The patient abided by the physican's recommendation of using corticosteroids before the chemotherapy, but still ended up developing atrial fibrillation (Huq, Balvanz, & Mambourg, 2018). There is less cardiac toxicity with the use of docetaxel than there is with paclitaxel, but the risk for heart damage is still there when using docetaxel because everyone is going to react differently to medications, especially those that can have very severe side effects, like congestive heart failure. Docetaxel seems to be better for the treatment of breast cancer compared to the anthracyclines because it has been demonstrated to increase the survival rate of those with cancer while also lessening the cardiotoxic effects on the heart; moreover, the drug was first used, specifically, for the treatment of metastatic breast cancer.

Alkylating Agents

Alkylating Agents are found both in the environment and in cells, as they are in pollutants such as tobacco smoke and are also byproducts in the body (Fu, Calvo, & Samson, 2012). These agents are dangerous to human health because of their effects, which include cytotoxicity, carcinogenic effects, and teratogenic effects; in spite of this, the agents are used as a chemotherapy to kill cancer cells (Fu, Calvo, & Samson, 2012). The alkylating agents are the oldest class of chemotherapies (Han, Zhou, & Liu, 2017). The United States released mustard gas, an alkylating agent, against the Germans in World War 2 (1943), which caused a major reduction in the number of white blood cells; furthermore, this led to the study of them as an anticancer agent (Iqubal, et al., 2019). They act on cancer cells by adding alkyl groups to the DNA; thus, the two strands of DNA are then cross-linked and prevented from replicating (Higgins, O'Halloran, & Chang, 2015). Risk factors associated with alkylating agents-induced cardiotoxicity include old age, combination therapy, and total single dose (Han, Zhou, & Liu, 2017).

DNA damage is induced when the alkylating agents react with DNA bases (Fu, Calvo, & Samson, 2012). When a certain alkylating agent is introduced to the body, the guanine at the N7-position on DNA, which has a high nucleophilic reactivity, is typically used to form N7-methyl guanine, a predominant methylation adduct (Figure 1); moreover, DNA alkylation lesions are formed and N7-methyl guanine is responsible for 60-80% of them (Fu, Calvo, & Samson, 2012). N7-methyl guanine itself is not cytotoxic, but it forms apurinic or apyrimidinic (AP) sites, which are places in the DNA where a purine or pyrimidine is not present on one side of the

double helix; furthermore, these sites are toxic (Fu, Calvo, & Samson, 2012). These base adducts can induce mutagenesis and/or inhibit the replication and transcription of DNA, which leads to cell death in both healthy cells and cancer cells (Fu, Calvo, & Samson, 2012).

A well-known alkylating agent used in the treatment of many cancers including lymphoma and breast cancer and autoimmune disorders is cyclophosphamide. When used in high doses for the treatment of cancer, permanent damage can be induced due to the heart developing structural injury (Madeddu, C. et al., 2016). Damage that could be induced includes congestive heart failure, myocardial depression, and cardiac tamponade, which is a fluid buildup between the pericardium (the sac surrounding the heart) and the heart muscle (Chakraborty, Bhattacharjee, & Kamath, 2017). Cardiac tamponade, as well as other damage, puts a lot of pressure on the heart, making it work harder; therefore, the heart will tire easier and will be susceptible to heart failure. Out of those who receive a high dose of cyclophosphamide, 20% has undergone acute cardiac dysfunction (Liu, et al., 2018). Using cyclophosphamide in high doses is thought to increase the risk of heart failure anywhere from 7-28% (Madeddu, 2016). This makes cyclophosphamide a type 1 chemotherapy and dependent upon dose. It is thought that free oxygen radicals play a role in the cardiotoxicity, but the exact mechanism as to how cardiotoxicity is induced is not known (Higgins, O'Halloran, & Chang, 2015).

Despite the classification of a type 1 chemotherapy, the odds of long-term cardiotoxicity induced by cyclophosphamide in a cancer patient are relatively rare and usually seen when the dosage is over 140 mg/kg before a bone marrow

transplant (Zamorano, et al., 2016). In 33% of patients undergoing bone marrow transplantation that were pretreated with cyclophosphamide, there were ECG changes showing QT prolongation and cardiac arrhythmias (Tamargo, Caballero, & Delpón, 2015). An ECG detects the electrical activity of the ventricles of the heart as it pumps blood throughout the body, and each wave is labeled as P, Q, R, S, and T, respectively. When the heart takes longer to recharge, or refill the ventricles with blood, it is termed a QT prolongation.

This change in the electrical activity of the heart can lead to arrhythmias. The use of cyclophosphamide has been linked to many different heart arrhythmias such as bradycardia, atrioventricular block, atrial fibrillation, supraventricular tachycardias, and ventricular tachycardia/fibrillation (Zamorano, et al., 2016). According to Tamargo, Caballero, and Delpón, 7.9-10% of patients administered with a high dose of cyclophosphamide show atrial and ventricular tachyarrhythmias 24-72 hours after the dose (abnormal rhythms in the upper or lower chambers of the heart, respectively); however, it disappears spontaneously within a 7-day time frame (2015). The cardiac manifestation that is most severe and occurs in less than 1-9% of those who used high doses of cyclophosphamide is hemorrhagic necrotic perimyocarditis (Emadi, Jones, & Brodsky, 2009). A 54-year-old women with normal heart function was given cyclophosphamide a month before her autologous stem cell transplantation to mobilize her peripheral blood hematopoietic stem cells, but within 24 hours after her surgery, she had succumbed to cyclophosphamide-induced cardiotoxicity (Martin, et al., 2017). According to Martin, et al., the autopsy of the woman's heart showed moderate hemorrhagic pericarditis and intra-cavity

thrombus (2017). This is consistent with the clinical presentation of cyclophosphamide-induced cardiotoxicity, which is congestive heart failure that occurs suddenly (Martin, et al., 2017). Cardiotoxicity is typically due to left ventricular function and occurs in 45% of those who undergo bone marrow transplants (Emadi, Jones, & Brodsky, 2009). Cyclophosphamide has been connected to apoptosis of the cardiomyocytes and damage of the mitochondria, as well (Iqubal, et al., 2019). Cyclophosphamide's metabolites induce the generation of reactive oxygen species in the mitochondria and cause the inflammation of heart cells (Iqubal, et al., 2019).

In a study using rat cardiomyocytes, the cells were grown overnight and exposed to one of the following: cyclophosphamide, 4-hydroxycyclophosphamide, carboxyethylphosphoramide mustard, or acrolein (Kurauchi, et al., 2017). Moreover, the cells that were exposed to 4-hydroxycyclophosphamide and acrolein for 24- and 48-hour periods showed myocardial cytotoxicity and higher levels of reactive oxygen species (produced in the mitochondria) than in the controls (Kurauchi, et al., 2017). This study manifested the notion that the cyclophosphamide itself was not cytotoxic, but the metabolites from the cyclophosphamide were causing the damage to the heart cells (Kurachi, et al., 2017). Acrolein is a metabolite of cyclophosphamide that is toxic and reactive; therefore, it modifies proteins substantially and induces myocardial injury (Madeddu, 2016). The 4-hydroxycyclophosphamide was converted to acrolein, creating a higher concentration of it in the cell and an even greater extent of damage to the cardiomyocytes (Kurachi, et al., 2017).

Phosphoramide mustard is also formed, which is a neoplastic agent that causes tumor death; hence, the use in the treatment of cancer (Iqubal, et al., 2019). As shown in Figure 2, 4-hydro-cyclophosphamide exists with aldophosphamide, which breaks down into phosphoramide mustard and acrolein in the body; moreover, the phosphoramide mustard is useful in the treatment of cancer while the acrolein formed, mentioned above, is toxic to the heart in many ways (Iqubal, et al., 2019). Acrolein activates caspases by forming an adduct, or bond, with cysteine, which then causes apoptosis of heart cells (Iqubal, et al., 2019). Acrolein also leads to oxidative stress making the heart work harder, and thus leading to heart failure, and potentially death (Iqubal, et al., 2019). As shown in Figure 2, the formation of acrolein will eventually lead to immune suppression, cardiac inflammation, endothelial dysfunction and vasoconstriction, or cardiac apoptosis (Iqubal, et al., 2019).

Cyclophosphamide is a chemotherapy that is also used before transplants; although this case is rare, it goes to show that even when used in small doses for transplants, cardiotoxicity could still be an unwanted side effect that can lead to death. The woman's heart was healthy going into surgery and all the scans were normal, but once the cardiotoxicity started, it could not be stopped from killing her. Cyclophosphamide seems to have a lower risk of irreversible damage to the heart, and it contains 2 elements of which one is cardiotoxic and the other has anticancer effects; moreover, research has shown greater promise in making cyclophosphamide a safer treatment option compared to the anthracyclines that have to be taken with something else to try to prevent or lessen the cardiotoxic

effects that are otherwise unavoidable. Cyclophosphamide has different metabolites that either have anticancer effects or cardiotoxic effects; therefore, creating a treatment that does not have the cardiotoxic effects of acrolein but has the anticancer effects of phosphoramide mustard, would be beneficial to many who are undergoing transplants and to those fighting their battle with cancer.

Tyrosine Kinase Inhibitors

Tyrosine kinases are enzymes that transfer phosphate onto amino acids from ATP, altering intracellular signaling pathways (Chaar, Kamta, & Ait-Oudhia, 2018). However, in many cancers, including breast cancer, the enzyme has been found to be overexpressed, and has led to the development of the Tyrosine Kinase Inhibitors, or TKIs (Chaar, Kamta, & Ait-Oudhia, 2018). The tyrosine kinase inhibitor binds to the tyrosine kinase receptor (TKR) preventing the proliferation of cells and enhancing apoptosis, but as with most chemotherapies, the TKIs have been tied to cardiotoxicity (Chaar, Kamta, & Ait-Oudhia, 2018). With TKI use, the way that cardiomyocytes are injured varies depending upon the specific TKI taken (Chaar, Kamta, & Ait-Oudhia, 2018). Some TKI's are not as toxic to the heart as others (Chaar, Kamta, & Ait-Oudhia, 2018). The difference in the mechanisms between the FDA approved TKIs (greater than 30) that make some toxic to the heart and others not toxic is still not understood (Brown, Ray, & Herrmann, 2019). Any pre-existing conditions such as cardiac disease, diabetes, and hypertension, and genetics all increase the chance of injury to the heart muscle when taking TKIs (Chaar, Kamta, & Ait-Oudhia, 2018).

TKIs have been associated with mitochondrial damage due to the inhibition of kinases that were not targeted, such as protein kinase A; moreover, this can lead to the hypertrophy of the cardiomyocyte (Chaar, Kamta, & Ait-Oudhia, 2018). QT prolongation, as mentioned with cyclophosphamide, has also been associated with TKI use (Chaar, Kamta, & Ait-Oudhia, 2018). Acute vascular events have been tied to TKI use, which can lead to hypertension and damage to the cardiomyocytes; in spite of this, not all TKIs induce hypertension (Hermann, et al., 2016).

The TKI lapatinib is a common chemotherapy used in the treatment of breast cancer. It targets the human epidermal growth factor receptor 2 and the epidermal growth factor receptor, and it has been speculated that the drug is toxic to the heart (Choi & Chang, 2017). When compared with other chemotherapies, though, the lapatinib-induced cardiotoxicity rate was low (Choi & Chang, 2017). The result of several studies showed no significant increase in the risk for heart issues (Choi & Chang, 2017). However, patients are still at risk, so there is still careful monitoring of the heart during the course of treatment (Choi & Chang, 2017). Because the incidences of those with lapatinib-induced cardiotoxicity are typically reversible and the risk of cardiotoxicity is low, it is Type II Chemotherapy (Jerusalem, Lancellotti, & Kim, 2019). The chance of the development of cardiomyopathy in a patient treated with lapatinib is 1-2% and for heart failure, the chance is 0.1-0.5%; furthermore, it has the lowest rate of cardiotoxicity (Brown, Ray, & Herrmann, 2019).

Lapatinib has shown to be an effective TKI against triple-negative breast cancer cells, as it triggers extensive DNA damage (Abo-Zeid, Abo-Elfadl, & Gamal-

Eldeen, 2019). Triple-negative breast cancer is an aggressive and invasive type of breast cancer that is difficult to treat (American Cancer Society, 2019). This type does not have estrogen receptors, progesterone receptors, or a lot of human epidermal growth factor receptors 2; hence, the name, triple negative (American Cancer Society, 2019). However, triple-negative breast cancer grows and spreads faster than other breast cancers while also having limited treatment options and a worse outcome (American Cancer Society, 2019).

Lapatinib has been thought to be effective as a single agent or in combination with other chemotherapies for those with breast cancer (Choi & Chang, 2017). Lapatinib activates the 5' adenosine monophosphate-activated protein kinase pathway; furthermore, this pathway inhibits the death of α-induced cardiomyocytes, so the therapy may have a cardioprotective effect (Choi & Chang, 2017). When paired with other chemotherapies such as trastuzumab and the anthracyclines, which induce cardiotoxicity, lapatinib may protect the heart from some of that damage. There is, however, a chance of developing cardiotoxicity with the use of lapatinib, but the overall incidence of it in those with breast cancer is low when compared with trastuzumab (Choi & Chang, 2017).

In a meta-analysis of 45 studies including patients treated with lapatinib, cardiotoxicity included left ventricular dysfunction and arrhythmias (Choi & Chang, 2017). In the studies, over 600 of the patients in 22 of the studies had cardiac adverse events and 58 people in 5 of the studies had left ventricular dysfunction (Choi & Chang, 2017). According to Choi & Chang, overall, 2.70% of those in the studies had left ventricular dysfunction, arrhythmia, LVEF (left ventricular ejection

fraction) decrease, and/or other cardiac adverse events (2017). LVEF is, with each contraction, the amount of blood pumped out of the heart. In a study of patients with breast cancer, 3.0% of them had cardiotoxicity (Choi & Chang, 2017). The risk factors associated with lapatinib-induced cardiotoxicity include previous treatment with anthracyclines, older than 65 years old, a high BMI, previous left ventricular dysfunction, arterial hypertension, and previous radiation therapy (Zamorano, et al., 2016). The effects of lapatinib on the heart when used to treat cancer is not fully comprehended and more research needs to be performed in order to better understand and verify the mechanisms of action of lapatinib and how it plays into the role of cardioprotective and cardiotoxic agents.

Antiestrogen

Antiestrogen is another class of chemotherapy that is used in the treatment of breast cancer. A study using older patients who survived breast cancer from Taiwan discovered that the use of antiestrogens decreased the risk of developing lung cancer later on in life (Chu, et al., 2017). Estrogen receptors (alpha and beta) safeguard the central nervous system and the cardiovascular system; however, they have also been involved in breast cancer and cardiovascular diseases (Traboulsi, et al., 2017). These receptors have been found to function in adult cardiomyocytes, and in a study performed on rats, the destruction of the estrogen receptor alpha promoted ischemia or reperfusion (Lorga, et al., 2017). Antiestrogens work by blocking the estrogenic signaling (Traboulsi, et al., 2017). These drugs act as steroids to compete for the estrogen receptors, and therefore, modify the activity of

the receptor (Traboulsi, et al., 2017). Antiestrogens compete with estradiol, a form of estrogen (the female sex hormone), for the estrogen receptor alpha site (Traboulsi, et al., 2017). In breast cancer cells that tested positive for the estrogen receptor alpha, there was an increased overall amount of estrogen receptor alpha due to the increase of the product produced by the ubiquitin-proteasome pathway (Traboulsi, et al., 2017).

Tamoxifen is a common chemotherapy in the antiestrogen class that is used to treat breast cancer. Tamoxifen opposes the proliferation of breast cancer cells; (Traboulsi, et al., 2017). Tamoxifen has been thought to have cardiovascular effects that are favorable; moreover, these effects include reducing total and low-density lipoprotein cholesterol levels while increasing the amount of "good" cholesterol, high-density lipoprotein (Khosrow-Khavar, et al., 2017). In a study comparing aromatic inhibitors to Tamoxifen, there was a 34% decreased risk of developing ischemic heart disease when treated with Tamoxifen rather than no treatment; furthermore, there was a 33% decrease in risk of developing any tamoxifen-induced cardiovascular events (Khosrow-Khavar, et al., 2017). Likewise, in breast cancer treatment, there was a 26% decreased risk of myocardial infarction and a 45% decrease in risk of death due to myocardial infarction (Khosrow-Khavar, et al., 2017). In a study of women with breast cancer who were either treated with anthracyclines or with tamoxifen displayed the protective effects that tamoxifen has on the heart, as the troponin 1 (protein that controls actin and myosin in the heart) levels stayed the same in the treatment group treated only with tamoxifen and in the group treated with both anthracycline and tamoxifen; on the other hand, the

group treated with only anthracyclines had an increase in the levels (Silva, et al., 2017).

PREVENTIVE STRATEGIES/TREATMENT OPTIONS

With the use of chemotherapies and the knowledge of the cardiotoxicity that comes with a majority of them, there are some treatment options to help prevent the cardiotoxicity that is induced. Potential treatments and preventative strategies include fullenerol, dexrazoxane, carvedilol, troponin, and statins.

Fullenerol has been studied intensely, and a lot of those studies have found that fullenerol can act as a protective agent to damage induced by the use of doxorubicin by functioning as a free radical scavenger (Potočnik, et al., 2017). Furthermore, there is no evidence of it interfering with the anti-cancer activity of doxorubicin (Potočnik, et al., 2017). In a study on rats with colon cancer, the development of adenocarcinomas was significantly reduced in the group treated with just doxorubicin and in the group treated with fullenerol before being treated with doxorubicin (Potočnik, et al., 2017). Therefore, fullenerol did not have an effect on doxorubicin treating cancer. Pretreating the rats with fullenerol also kept oxidation at a normal level, while doxorubicin increases oxidative stress in the heart (Potočnik, et al., 2017). Furthermore, the ECGs of rats pretreated were normal while those just treated with doxorubicin show lengthening in the QRS and ST waves (Potočnik, Perše, Cerar, Injac, & Finderie, 2017). Doxorubicin-induced cardiotoxicity is prevented by the pretreatment of fullenerol, as it acts as a cardioprotective agent and resists any changes that doxorubicin tries to induce (Potočnik, et al., 2017).

Dexrazoxane is an iron-chelating agent that reduces cardiotoxicity induced by anthracyclines significantly for solid tumors in adults and for leukemia and Ewing's sarcoma in children (Curigliano, et al., 2012). Dexrazoxane is also a Topoisomerase IIβ inhibitor, and it is the most studied for protection against anthracycline-induced cardiotoxicity; furthermore, it does so without inhibiting the anticancer effects of the anthracycline treatment (Higgins, O'Halloran, & Chang, 2015). The American Society of Clinical Oncology recommends the use of Dexrazoxane for breast cancer to act as a cardioprotectant against the toxicity induced by doxorubicin (Curigliano, et al., 2012). Dexrazoxane is only recommended, though, if the patient has received over 300 mg/m^2 of doxorubicin (Higgins, O'Halloran, & Chang, 2015). A meta-analysis of adult patients treated with anthracyclines demonstrated a reduced risk of heart failure when taking dexrazoxane (Zamorano, et al., 2016). In children, dexrazoxane was found to protect the heart without compromising the anticancer effects of chemotherapies; likewise, in another study, the development of cardiotoxicity in the future was much higher in those who were not treated with dexrazoxane (Reichardt, et al., 2018). Overall, dexrazoxane is a promising preventative strategy against the cardiotoxicity that is induced by chemotherapies, specifically, the anthracyclines and doxorubicin.

Carvedilol is a beta-blocker that has also been thought to prevent any cardiac damage also induced by doxorubicin (Curigliano, et al., 2012). A study confirmed that it prevents left ventricular dysfunction and has reduced mortality in those taking doxorubicin (Curigliano, et al., 2012). Carvedilol has also been shown to maintain calcium homeostasis, which is vital to the contraction of the heart muscle,

and decrease oxidative stress (Godishala, Yang, & Asnani, 2018). Beta-blockers have anti-apoptotic and antioxidant effects, which decrease the damage to the mitochondria (Godishala, Yang, & Asnani, 2018). In another study performed on patients with HER2-negative breast cancer showed that there was no cardiotoxicity or decrease in left ventricular ejection fracture to 35% among the group treated with carvedilol (Avila, et al., 2018). HER2-negative breast cancer does not have an excess of the human epidermal growth factor receptor 2 meaning that the cancer does not respond to chemotherapies that target HER2 (American Cancer Society, 2019). More research on carvedilol is needed to determine if it would be a preventative strategy that would save cancer patients from cardiotoxicity.

Troponin has been demonstrated to detect chemotherapy-induced cardiotoxicity long before the drug has had a chance to decrease the left ventricular ejection fraction (Curigliano, et al., 2012). In patients treated with trastuzumab, troponin has been determined to distinguish between reversible and irreversible damage induced; moreover, this is determined by the detection of myocardial cell necrosis (Curigliano, et al., 2012). The increase of troponin levels demonstrated, in a study with 114 patients who received a high dose of chemotherapy, a lower incidence of cardiotoxicity in the future (Zamorano, et al., 2016). Monitoring the levels of troponin in the body during the chemotherapy treatment may help determine which patients are at risk for chemotherapy-induced cardiotoxicity in the future.

Statins are cholesterol medications that decrease the cell's synthesis of intrinsic cholesterol and promote the uptake of serum LDL cholesterol, and they

may be just as potent as other cardiotoxic preventative medications, such as dexrazoxane (Henninger & Fritz, 2017). There was a stronger cardioprotective potential in those animals treated with statins than in those treated with carvedilol (Henninger & Fritz, 2017). They have also shown to decrease oxidative damage; furthermore, the statins stabilize the mitochondria and decrease the vascular inflammation (Higgins, O'Halloran, & Chang, 2015). Statins may interfere with NADPH oxidase, which hinders the toxicity induced by anthracyclines (Henninger & Fritz, 2017). However, these effects were only studied on acute toxicity, so more studies are needed for those who develop chronic cardiotoxicity (Henninger & Fritz, 2017). One study performed did demonstrate that statins have the potential to prevent cardiotoxicity induced by doxorubicin whether the toxicity was acute, subacute, or chronic (Henninger & Fritz, 2017). Furthermore, a study in 2012 of breast cancer patients receiving statins during the course of their chemotherapy displayed a significantly lower risk of heart failure (Henninger & Fritz, 2017). Statins have also demonstrated their ability to improve the anti-tumor efficiency of doxorubicin (Henninger &Fritz, 2017). The use of statins during the course of chemotherapy seems to be cardioprotective and would be great for those enduring the harsh chemotherapy treatments.

CONCLUSION

Chemotherapies are widely used in the treatment of cancer, and although they have anticancer effects, the drugs are so potent, that they are also affecting the heart. There are many classes of chemotherapies and some are more potent than

others. Anthracyclines are among the most well-known chemotherapies due to the wide range of cancers they are used to treat, but they also tend to induce irreversible damage to the heart that ultimately leads to heart failure and death. Monoclonal antibodies are known for their cardioprotective effects on the heart. There are many classes of chemotherapies that fall between the anthracyclines and the monoclonal antibodies on the cardiotoxicity scale. Trastuzumab is among those drugs that typically cause reversible damage to the heart, unless it's given in addition to an anthracycline or given too soon after anthracycline treatment.

Cancer, unfortunately, is a particularly prevalent disease, so the effects of the treatment used is of utmost importance to those who fight the difficult battle and come out alive. For someone to survive cancer and chemotherapy only to end up with chemotherapy-induced cardiotoxicity, that is still losing to cancer. Although, the person survived cancer the first time around, it is ironic that even then, cancer still wins because the treatment used is harmful. This brings about the importance of weighing the risks of all the different chemotherapy options and deciding which would be best considering the chemotherapy's ability to kill cancer cells while also avoiding irreversible damage to the heart. It also puts pressure on drug companies and scientists to create a drug that is safer than current chemotherapies or something that can be used to help prevent cardiotoxicity as the chemotherapy is being used. Cancer has been around for so long, and there is still not a medication that can treat it without causing other complications. A preventative medication that has extensive research and has been shown to decrease the cardiotoxic effects that chemotherapies, and specifically, anthracyclines, have on the heart is dexraxozone.

Carvedilol, statins, and troponin I are both being researched to prevent and detect chemotherapy-induced cardiotoxicity. Creating a treatment that is safe and effective when fighting cancer will improve the lives of many who are able to win their battle against cancer.

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