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Drug-Induced Cardiotoxicity of Oncological Agents: Monitoring Parameters, Prevention, and Future Chemotherapy

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CONTINUING EDUCATION

Drug-induced Cardiotoxicity of Oncological Agents: Monitoring Parameters, Prevention, and Future Chemotherapy

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Goal:

The goal of this article is to educate pharmacists of the impact of cardiotoxicity on chemotherapy regimens including key cancer agents, monitoring parameters, prevention, and the future of chemotherapy..

Objectives for Pharmacists:

At the conclusion of this lesson, successful participants should be able to:

1. Determine the clinical significance of cardiotoxicity in cancer therapy.
2. Describe the mechanism of action and cardiotoxic effects of anthracyclines, mitoxantrone, trastuzumab, 5-fluorouracil, and bortezomib.
3. Compare the cardiotoxicity safety profiles of the different HER2 inhibitors and their roles in HER2 positive breast cancer
4. Evaluate the treatment options, monitoring parameters, and prevention of anti-cancer drug-induced cardiotoxicity.

Objectives for Technicians:

#1-3 above (same as pharmacists)

4. Describe the treatment options, monitoring parameters, and prevention of anti-cancer drug-induced cardiotoxicity.

Introduction

Cancer is the second leading cause of death in the United States, with a 5 year survival rate of 68%. This accounts for 1 in 4 deaths in the US. In 2013, 1.6 million Americans were diagnosed with cancer, and approximately 585,720 Americans are expected to die in 2014 from cancer.[1] Due to developments in early diagnosis and therapies, cancer survival rates have greatly improved. Emerging anti-cancer drugs have been increasingly valuable in treatments of many cancers and have made significant advances in the field of oncology. However, a caveat of many of the widely used, highly effective agents is that they are associated with cardiotoxic effects; this increases cardiovascular morbidity in patients on these regimens. Anti-cancer drugs target cell signaling pathways, which inadvertently affect myocardial cells. Because of this, there has been a development of cardio-oncology, which is aimed at cardiovascular care for oncology patients. This new focus is highly relevant in the treatment of cancers as the cardiotoxic effects have led to the discontinuation of many regimens, which have been shown clinically to slow tumor growth and lead to remission otherwise. Drugs which are highly associated with cardiotoxic side effects include anthracyclines, mitoxantrone, trastuzumab, and 5-fluorouracil. The cardiotoxic effects of these agents differ based on their target and mechanism of action. Hence, pharmacists must be aware of these myocardial toxic effects to effectively monitor cardiac function of oncology patients under their care. As the incidence of myocardial side effects increases and are taken into account in the treatment of many cancers, promising developments of newer anti-cancer agents have arisen for the discipline of cardio-toxicity including: lapatinib, pertuzumab, and trastuzumab emtansine.

Anthracyclines

Anthracyclines are a class of cytotoxic antibiotic commonly used to treat cancer. The class includes the drugs: daunorubicin (DaunoXome, Cerubidine), doxorubicin (Doxil, Adriamycin, Lipodox), epirubicin (Ellence), idarubicin (Idamycin), and valrubicin (Valstar). They work by inhibiting DNA and RNA synthesis through direct binding to DNA in addition to inhibiting DNA repair.[2] Consequently, the lack of functional DNA and RNA deprives malignant cells of basic resources for survival, a useful property of an anti-cancer agent. Liposomal formulations of anthracyclines, such as Doxil and Lipodox, are generally the preferred analogue due to its accumulation and releasing properties. Their advantages stem from their properties of preferential accumulation and prolonged release within the tumor environment; thus, lowering accumulation in healthy tissue and adverse effects.[3] Although anthracyclines are beneficial in cancer treatment, it also has concerning adverse effects such as cardiotoxicity, cardiomyopathy, declined left ventricular ejection fraction (LVEF), and congestive heart failure (CHF).[4] An alarming factor is that anthracycline-induced cardiotoxicity is dose-related and tends to be progressive and irreversible, which can add undesirable complications to vulnerable cancer patients.[5] Therefore, cardiotoxicity is a major limitation in the usage of anthracycline in the treatment of cancer, requiring critical monitoring and evaluation within an interdisciplinary setting of pharmacists and oncologists.

Anthracycline-induced cardiotoxicity can be categorized into three types. The first type is the acute or sub-acute injury that may occur immediately after treatment. This type is more rare and includes conditions such as transient arrhythmia, pericarditis-myocarditis syndrome, or acute failure of the left ventricle.[6] The second type is chronic cardiotoxicity,

the more common and clinically important form of damage, which includes cardiomyopathy.[6] The third type of cardiotoxicity manifests years after treatment, leading to late-onset arrhythmia and ventricular dysfunction.[6] The exact cause of anthracycline-induced cardiotoxicity is uncertain but the proposed mechanisms include reactive oxygen species (ROS) leading to membrane damage, lipid peroxidation, cardiomyocyte apoptosis or necrosis, disruption of sarcomere structure, or altered ability of cardiac myocyte contraction.[5]

When the anti-cancer benefits of anthracycline outweigh the risks of cardiotoxicity, the common methods to monitor patient's conditions throughout treatment include an echocardiography (ECHO) and multiple gated acquisition (MUGA) scan. ECHO measures LVEF and indicates cases of left ventricle dysfunction (LVD) that denotes anthracycline-induced cardiotoxicity. However, ECHO may be regarded as insensitive in detecting cardiotoxicity at an early stage due to the fact that significant changes in LVEF usually presents upon substantial myocardial damage. On the other hand, a normal LVEF does not exclude the possibility of cardiotoxicity in the future. Usually, an LVEF less than 50% or a LVEF decrease of 10% or greater from baseline constitutes for discontinuation of the anthracycline. On the other hand, the MUGA scan measures cardiac function but it has the disadvantage of radioactivity exposure and limited information on cardiac structure and diastolic function.[7]

There are many risk factors for anthracycline-induced cardiotoxicity that pharmacists and oncologists should be aware of. The biggest risk factor is exceeding the recommended maximum cumulative lifetime dose of anthracyclines. Others include prior anthracycline treatment, concurrent use of other cardiotoxic agents, history of cardiovascular disorders, older and younger age, and female gender.[5] As anthracycline cardiotoxicity is progressive and irreversible, it is critical to know the maximum cumulative dose of the specific anthracycline utilized. The recommended lifetime cumulative doses according to the package inserts are 550 mg/m2 for doxorubicin[8], 400 mg/m2 for daunorubicin[9], and 900 mg/m2 for epirubicin in adults.[10] However, pediatrics is a special vulnerable population that even the smallest dose of anthracycline may induce cardiac complications.[11] In addition, cardiotoxicity of anthracyclines is peak-related. Therefore, utilizing continuous infusions (24-48 hours) as opposed to bolus administration (5-15 minutes) will lower peak serum concentration and decrease the risk of acute cardiotoxicity.[11]

Once anthracycline-induced cardiotoxicity is present in a patient, preventative care should be implemented to prevent the condition from worsening and recurring. A common secondary prevention measure is a cardioprotective intravenous agent, dexrazoxane (Totect, Zinecard). The proposed mechanism of dexrazoxane is the metal chelation that reduces anthracycline-induced free radical damage. Two meta-analyses have shown that dexrazoxane significantly decreases the risk of anthracycline-induced cardiotoxicity in cancer patients by approximately 75% compared to no treatment.[12] Dosing of dexrazoxane to anthracycline is a 10:1 ratio, respectively. Although dexrazoxane is a common cardioprotective agent, there is insufficient evidence to recommend its use for pediatric patients.[12]

Mitoxantrone

Mitoxantrone (Novantrone) is an anthracenedione derivative, a relative of the anthracyclines. Its mechanism of action is similar to anthracyclines in that it intercalates into DNA and causes DNA strand break in addition to inhibiting DNA topoisomerase II and prevents DNA replication.[2] Mitoxantrone is also associated with dose-related cardiotoxicity such as tachycardia, arrhythmia, and CHF. The risk of cardiotoxicity increases with increased cumulative lifetime dose of mitoxantrone, prior anthracycline treatments, prior mediastinal radiotherapy and pre-existing cardiovascular disease.[13] Therefore, mitoxantrone treatment is not recommended in patients with LVEF < 50% or with clinically significant reduction in LVEF while on treatment.[14] Mitoxantrone is indicated for multiple sclerosis and has a maximum lifetime cumulative dose of 140 mg/m2.[14] It is administered every 3 months as a short IV infusion (5-15 minutes) as opposed to subcutaneous, intramuscular, intrathecal, and intra-arterial administrations, which are contraindicated.[14] Baseline LVEF should be obtained prior to initiation of mitoxantrone therapy and continually monitored throughout treatment. Mitoxantrone is metabolized by the liver and reduces the amount of leukocytes. Therefore, it is not recommended in hepatic insufficiency with three-fold elevated enzymes or when neutrophil count is < 1500 mm3. Consequently, complete blood count and liver function tests should be done prior to each administration. Mitoxantrone's side effects include blue-green urine days after infusion, sterility, and birth defects, which warrant for contraception throughout treatment and contraceptive test prior to each administration.[15] Similar to anthracycline, dexrazoxane may be utilized to reduce free radical damage of mitoxantrone-induced cardiotoxicity with a dosing of dexrazoxane to mitoxantrone at 50:1 ratio.[16]

Human Epidermal Growth Factor Receptor 2 Protein (HER-2) receptor antagonist: trastuzumab

HER-2 receptor antagonists are humanized IgG1 kappa monoclonal antibodies that target the human epidermal growth factor receptor tyrosine kinase HER-2/ErbB2 for use in chemotherapy. Their effect on the over-

expression of HER-2 is due to their selective binding to the extracellular HER-2. In recent years, these agents have been widely used in the treatment of women with HER2-positive breast cancer. However, while useful, their implications in cardiomyopathy and other cardiotoxic effects have limited their use. Trastuzumab is a HER-2 receptor inhibitor that has the most implications with cardiotoxicity in patients.[18]

Trastuzumab is one of the older HER-2 receptor antagonists that have been associated with cardiotoxicity. Using the classification system from the New York Heart Association (NYHA) to classify heart failure, the American Heart Association (AHA) found that HER-2 receptor antagonists have been associated with cardiotoxicity as its most debilitating side effect.[18] The use of trastuzumab in HER2-positive breast cancer patients revealed cardiac dysfunction to a large extent shown in a large phase III trial.[18] The incidence of cardiac dysfunction ranged between 4% to 7% when trastuzumab is used in monotherapy. However, if combined with anthracyclines, this number can reach up to 27%.[18] Cardiac dysfunction in trastuzumab includes decreased LVEF and LVD. The rate of heart failure in patients treated with trastuzumab was significantly higher than those with regimens which did not include trastuzumab.[19] Risks of cardiotoxicity of trastuzumab increases when anthracyclines are used in conjunction with or prior to the administration of trasuzumab.[18] Hence, more careful monitoring for cardiac function is required for patients on these combinations.

While it is clear that the use of trastuzumab is related to cardiac failure, the mechanism of cardiotoxicity is unclear. Erb2 is associated in a pathway that is essential for cardiomyocyte growth, repair, and survival. The mechanism of trastuzumab is currently thought to be related to its inhibition of the signaling cascade of the epidermal growth factor that includes cardiomyocyte HER-2 signaling and its ligand neuregulin-1. Neuregulin-1 and ErbB4 binding increases the activity of the tyrosine kinase, leading to hetero-dimerization with Erb2. This increases the signaling potency, which controls the survival of cardiomyocytes. Interruption of this signaling cascade can result in an ineffective mounting of a stress response.[18]

Unlike anthracyclines, cardiotoxicities of HER-2 receptor antagonists has not been linked to cell death. Rather, cardiotoxic stress from these agents is more closely associated with cardiac dysfunction. Moreover, it is important to note that the cardiotoxic effects of HER-2 receptor antagonists is not cumulative-dose related. Upon observation using electron microscopy, typically ultrasound changes were not present. This indicates that the cardiotoxic effects are reversible upon discontinuation of the agents. However, patients do not demonstrate recovery by a full 100%.[19]

To ensure patient safety on trastuzumab, baseline cardiac function is performed prior to therapy using chemotherapeutic medication. Assessment of this is completed using MUGA and ECHO. Patients with normal cardiac function will be allowed to proceed with therapy with trastuzumab. These are patients with normal LVEF (55-70%). Those with intermediate risk factors may begin treatment, but must be under increased observation of their health-care provider to determine the risk-benefit relationship. Intermediate risk factors are those with borderline LVEF (40-50%), advanced age, and increased cardiac risk.[19]

During treatment, patients' LVEF is closely monitored and their treatment is based on the decrease of LVEF. In patients exhibiting a normal ejection fraction (EF) with an absolute decrease of greater than 16%, it is recommended for the treatment to be held for four weeks. If EF falls below the normal range, any decrease greater than 10% from baseline is indicative that treatment should be held for four weeks. It is noted that these decreases are symptomatic decreases of LVEF.[19]

Promising HER-2 inhibitors: lapatinib (Tykerb), pertuzumab (Perjeta), and trastuzumabemtansine (Kadcyla)

HER-2 positive breast cancers are associated with a poorer prognosis. Because of the high cardiotoxicity of trastuzumab that limits its use in chemotherapy, there are several recent developments in the treatment of HER-2 positive breast cancers. Newer agents used after failure or discontinuation of trastuzumab include lapatinib (Tykerb), pertuzumab (Perjeta), and trastuzumab emtansine (Kadcyla). These agents are accompanied with a lower rate of cardiotoxicity.

Lapatinib is a reversible inhibitor of HER-2 and epidermal growth factor receptor (EGFR). Its approved indication is in combination with capecitabine (Xeloda) following trastuzumab failure.[20] Lapatinib therapy is associated with a significantly lower rate of heart failure. While cardiotoxicity is seen in animal trials, the bright outlook of lapatinib in terms of cardiotoxicity remains that its mechanism does not affect the ErbB2-ErbB4 signaling pathway, which is activated by cardiac cells via neuregulin-1. Because of this, lapatinib has exhibited a low cardiotoxic profile in comparison to trastuzumab, as seen in preliminary data from clinical trials.[21]

Pertuzumab is a newer agent in the anti-ErbB2 family of drugs, which is indicated for HER2-positive breast cancer in patients who cannot tolerate or have failed trastuzumab. Similar to lapatinib, pertuzumab's mechanism does not involve the ErbB2-ErbB4 signaling pathway, which plays a role in its lower cardiotoxicity when compared to trastuzumab.[14] Additionally, the mechanism of action of pertuzumab differs from that of trastuzumab in that they recognize different epitopes distant from one another, which is thought to play a role in their difference in cardiotoxic safety profile.[21]

Trastuzumab emtansine (T-DM1) is a combination drug, which includes trastuzumab and mertansine (DM1). Mertansine is a potent cytotoxic derivative of

the antimicrotubule agent maytasine.[22] The promising cardiotoxic profile of T-DM1 is linked with the stability of the tioether linker (N-maleimidomethyl) cyclohexan-1-carboxylate (MCC), which covalently binds trastuzumab and DM1.[22] T-DM1's more favorable safety profile is associated with its mechanism of action. The agent is initially internalized into its target cell, where it covalently binds to a lysine, creating a positively charged Lys-MCC-MD1. Lys-MCC-MD1 is unable to diffuse past the membrane into nearby normal cells. Because of this, T-DM1 exudes lower cardiotoxicity than trastuzumab.[23] In addition to its free drug counterpart, trastuzumab, T-DM1 shows a higher cytotoxicity by delivering a higher drug concentration into the HER-2 positive tumor. In a phase II clinical trial, T-DM1 exhibited low cardiotoxicity, with no dose reduction due to decreased cardiac function. While it is noted that the pre-screened patient study population had low cardiotoxic potential, they continued receiving the agent for longer than one-year span. This is indicative of a tolerable long-term administration of T-DM1. In both phase I and phase II studies, cardiotoxicity was not reported with T-DM1.[23] Because of its lower cardiotoxic profile, T-DM1 is a promising new agent in HER-2 positive breast cancers in patients who discontinue trastuzumab regimens due to its toxic effect on the heart. However, T-DM1 show dose-limiting thrombocytopenia, which should be monitored in patients with moderate to high risk.[23]

5-Fluorouracil

5-fluorouracil (Adrucil) and its pro-drug capecitabine, are pyrimidine antagonist antineoplastic agents under the anti-metabolite family indicated in cancers of the breast, colorectal, gastric, pancreas, anal, bladder, cervix, bladder, esophagus, head and neck, and hepatobiliary pathway. While used for many indications, 5-fluorouracil (5-FU) has a several cardiac complications, including heart failure, arrhythmia, and myocardial ischemia.[11] The cardiotoxic effects of 5-FU is seen more in patients with a history of cardiac event and is reversible upon discontinuation of the agent.[24]

Similar to trastuzumab, the mechanism of toxicity of 5-FU is unknown. It is theorized that 5-FU induces coronary spasms and direct vasoconstriction on smooth muscle cells.[25] However, regardless of this theory, calcium channel blockers and nitrates were not seen as beneficial preventative agents for the cardiotoxic events. Another theory for 5-FU's cardiac adverse effects is that it is catabolized to fluoroacetate, which is a known cardiotoxic substance.[26]

One important study by Lamberti et al. showed cardiotoxic effects not only in cancer patients, but also in their providing healthcare workers who were exposed to the chemo-agents. The cause of the providers' decreased cardiac function was not studied, but a correlation exists between their level of myocardial dysfunction and the drug concentration of their working tables, floors, and air-conditioning. This indicates safety and prevention should be performed in both patients and their health care providers handling the drug.[26]

Additionally, the direct cardiotoxic effects of 5-FU are administration dose and frequency related. While continuous infusion and bolus dosing are both cardiotoxic, bolus dosing is associated with a lower cardiotoxic risk when compared to a prolonged continuous infusion regimen.25 24-hour 5-FU continuous infusions was associated with increased cardiac-related events when administered for 5 days, when compared to a shorter 5-FU administration regimen.[26]

Regardless of the dosing differences and mechanism of cardiotoxicity, all findings in the Lamberti study indicates 5-FU increases oxidative stress on cardiomyocytes, which can further lead to apoptosis of cardiac cells. Thus, the close cardiac monitoring must be considered in all patients on a cancer regimen utilizing 5-FU.

Proteasome Inhibitors

Bortezomib (Velcade) is a reversible dipeptide boronate-proteasome inhibitor used for hematological malignancies. Bortezomib has been shown to cause cardiotoxicity in patients, and thus studies have recently been performed to test for these toxic events. While these studies do not show this agent to induce cardiac myocyte death, it does show to cause impairment in cardiac function. Studies suggest that bortezomib impairs the ubiquitin-proteasome function, which is crucial in the vitality of cardiac myocytes. Thus, the inhibition of this proteasome pathway leads to cardiac dysfunction. The mechanism involves increased cardiac stress due to the accumulation of poly-ubiquinated proteins. Additionally, this agent impacts the heart possibly due to its induction of mitochondrial defects, leading to mitochondrial protein translocation. Further studies are needed to confirm this mechanism of toxicity. In a systematic review and meta-analysis by Xiao et al, there was no significant all-grade or high-grade cardiotoxicity risk with bortezomib.[21] Regardless, the cardiotoxicity of bortezomib has not been shown to be reversible, therefore monitoring should be performed in these patients with a high baseline cardiac toxicity risk.[27]

Conclusion

Oncologic drug-induced cardiotoxicity is a culprit in the premature halt of oncologic treatment regimen and induction or worsening of preventable cardiotoxicity. It not only hinders the treatment and progress of vulnerable oncologic patients, but it can potentially cause fatal or irreversible cardiac adverse events. Therefore, pharmacists uphold the crucial responsibility in recognizing high-risk patients, screening patients prior to treatment, monitoring ECHO and MUGA, documenting cumulative dose when necessary, and

utilizing cardioprotective agents when applicable, in an effort to avert drug-induced cardiotoxicity. Oncologic patients are already in a highly vulnerable state; therefore, hopeful goals of pharmacologic treatment and management should be to improve patients' quality of life and/or disease state, and at the very minimum to not harm the patients. As drug experts, pharmacists can make an impactful difference in preventing drug-induced cardiotoxicity in oncologic patients to optimize patients' treatment outcome and quality of life.

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