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Case Report

CHEMOTHERAPY INDUCED CARDIOTOXICITY: ICU PERSPECTIVE

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Introduction:

Venous vascular events (VE) are frequently diagnosed during cancer chemotherapy treatment. The arterial VE are uncommon and can be life threatening if incorrectly diagnosed and treated. Arterial ischemia uncommonly occur secondary to chemotherapy in coronary, cerebral and extremities vessels. Basically, arterial ischemia can be related to vasospasm phenomenon or occurrence of thrombosis[1].

Cardiotoxicity is a well-known side effect of several cytotoxic drugs, especially of the anthracyclines. The mechanism of anthracycline induced Cardiotoxicity seems to involve the formation of free radicals leading to oxidative stress. Other cytotoxic drugs such as 5-fluorouracil, cyclophosphamide and the taxoids are associated with Cardiotoxicity as well, although little is known about the possible mechanisms. Recently, it appeared that some novel cytotoxic drugs such as trastuzumab and cyclopentenyl cytosine also show cardiotoxic side effects[2].

Antineoplastic agents are associated with cardiac toxicities ranging from acute and delayed cardiomyopathy to myocardial ischemia. Although the risk of Cardiotoxicity due to anthracyclines and 5-fluorouracil is well recognized, descriptions of cardiac events associated with platinum agents are less common[3]. The use of cardiotoxic agents should be spared in patients with known coronary disease. They can be used in special situations after considering the risk versus benefit ratio and taking patient's consent. The use of cardiotoxic agents in patients with established cardiovascular risk factors (but without coronary artery disease) is more challenging[4].

Cardiotoxic effects can occur immediately during administration of the drug, or they may not manifest themselves until months or years after the patient has been treated. Cardiovascular toxicity can be reflected in preclinical and clinical events. Preclinical toxicity may be detected by histopathological or biochemical techniques; for example, doxorubicin-induced myocardial damage may appear in endomyocardial biopsy specimens but may not produce any measurable rise in troponin T or I protein levels[5].

Case Report:

26 year old married lady with no vascular co-morbidities presented with dysgerminoma (malignant germ cell tumor) with no distant organ metastasis. She received first cycle neo-adjuvant chemotherapy (NACT), BEP (Bleomicin, Etoposide and Cisplatin) regimen without any complications. One month later while receiving second cycle of BEP on fourth day of the treatment, she presented with anterior chest pain and dyspnea on exertion. On examination, her heart rate was 110 beats/min, her blood pressure was 160/110 mmHg. On auscultation there were no abnormal sounds or murmur.

An electrocardiogram (ECG) was done which showed ST-elevation s/o antero-lateral myocardial infarction and Echocardiography showed left ventricular LV) lateral wall hypokinesia, with estimated LV ejection fraction (EF) of 30%. Cardiac enzymes including Troponin-I was positive. She was managed in ICU with vasodilators, anticoagulants, antiplatelet medications and thrombolysed with streptokinase resulting in symptomatic relief and 50% reduction in ST elevation within one hour.

Coronary angiogram done 3 days later showed complete block in left anterior descending (LAD) artery following which angioplasty was advised. She recovered with medical treatment and discharged from hospital in stable condition.

Discussion:

The common Antineoplastic drugs associated with Cardiotoxicity include 5-fluorouracil (5-FU), Cisplatin, Vinca

alkaloids and BEP regimen (bleomicin, etoposide and cisplatin). Anthracyclines derivatives like doxorubicin, daunorubicin and epirubicin are reported to be associated with long term cardiac dysfunction. The mortality rate among patients who actually develop late Cardiotoxicity has been estimated to be high. The Risk Factors for Developing Cardiovascular Complications may be attributed to drug itself and to the patient receiving these drugs[6].

Drug related risk factors:

The dose of the drug administered during each session, cumulative dose, Molecular site of action, schedule of delivery, route of administration, combination of drugs given, and sequence of administration of these drugs are some important drug-related factors to consider[7].

Patient related risk factors:

These include age, previous cardiovascular disease, Prior mediastinal radiation therapy, metabolic abnormalities, demographics of the patient and hypersensitivity to the drugs given.

Some chemotherapeutic agents evoke Cardiotoxicity only when the drug is administered at high doses; examples include CHF and pericarditis with platinum drugs, atrial fibrillation with melphalan, systolic dysfunction and pericarditis with cyclophosphamide, and LV dysfunction with anthracyclines[8]. Ifosfamide causes low-grade arrhythmias at doses of 1.2 to 2 g/m2 per day for 5 days, but it causes CHF at doses of 10 to 18 g/m2. The cardiac side effects of anthracyclines and cyclophosphamide also depend on the schedule of administration. Administering anthracyclines by continuous infusion over 24 to 92 hours rather than by rapid intravenous infusion could reduce the cardiotoxicity of these drugs. Busulfan causes tachyarrhythmias, hypertension or hypotension, and LV dysfunction when injected but not when taken orally. Changing the sequence in which drugs are administered can also reduce cardiotoxicity. For example, the combination of IL-2 and interferon significantly increases hypotension, but delivering interferon alone for the first 2 weeks followed by IL-2 has much less cardiovascular toxicity[9].

The combination of paclitaxel and doxorubicin caused CHF in 20% of cases if the interval between doxorubicin and paclitaxel was 15 to 30 minutes, but increasing the interval to 4 to

16 hours reduced the Cardiotoxicity of this combination. Advanced age is a known risk factor for anthracycline Cardiotoxicity, as is previous cardiovascular disease. Infrequently, cardiovascular side effects from a particular drug occur in a specific subset of cancer patients; examples are cardiovascular complications from Cisplatin only in patients with metastatic testicular cancer, episodes of cardiotoxicity from low-dose Ifosfamide being more common in patients with lymphoma, and Alemtuzumab being associated with LV dysfunction in patients with mycosis fungoides[10].

Most of the chemotherapeutics will cause the myocardial ischemia by non atheromatous mechanism. Other possible pathological mechanisms may include direct endovascular damage, decreased activity of anticoagulant protein C, elevated plasma Von Willebrand factor level and

Hypomagnesemia[11].

The Cardiotoxicity associated with individual drugs is being briefly discussed here.

Anthracyclines/Anthraquinolones

Anthracyclines are the best studied of the anticancer drugs with established Cardiotoxicity. The Food and Drug Administration approved anthracyclines are doxorubicin, daunorubicin, and epirubicin. Acute Cardiotoxicity may manifest as nonspecific ST-segment and T-wave abnormalities. The mechanism is thought to be direct myocardial injury due to formation of free radicals. The prevalence of cardiotoxicity increases significantly when patients are given doses of doxorubicin >550 mg/m2. Mitoxantrone, a derivative of the anthracyclines, can cause mild Cardiotoxicity that is similar to that caused by anthracyclines at currently used dosages[12].

Alkylating Agents:

Although cyclophosphamide is relatively well tolerated at lower doses, when the cumulative dose exceeded 600 mg it may cause acute Cardiotoxicity. Prior treatment with an anthracycline and mediastinal radiation therapy has also been proposed as contributing factors to acute toxicity. Subsequent cardiac adverse events may include heart failure, myocarditis, or pericarditis. The mechanism of injury is thought to be related to endothelial and myocyte injury mediated through a toxic metabolite. Acute toxic effects can last up to 6 days. Ifosfamide is also known to cause dose-related incidence of heart failure and arrhythmia. Acute clinical syndromes associated with Cisplatin infusion include chest pain, palpitations and occasionally, elevated cardiac enzymes indicative of myocardial infarction (MI). A subset of patients receiving Cisplatin in combination with cyclophosphamide has developed heart failure; the risk was greatest among those of advanced age or with prior mediastinal irradiation. Cisplatin is unique in that it can cause late cardiovascular complications such as hypertension, LV hypertrophy, myocardial ischemia, and MI as long as 10 to 20 years after the remission of primary neoplastic disease for which it was given. Nephrotoxicity, experienced by up to 35% of patients receiving cisplatin, can lead to significant hypomagnesemia and hypokalemia, which in turn can cause cardiac arrhythmias[13].

Antimetabolites

The most commonly described cardiotoxic effect of 5-fluorouracil (5-FU) is the ischemic syndrome, which varies clinically from angina pectoris to acute MI. A “rechallenge” with 5-FU frequently reproduces the clinical Cardiotoxicity. The ischemia is usually reversible on cessation of the 5-FU

and implementation of anti-ischemic medical therapy. Ischemia can occur in patients without underlying coronary artery disease (CAD) (incidence, 1.1%), but the incidence is higher in patients with CAD (4.5%) [14].

Antimicrotubule Agents

Paclitaxel has recently been used to coat stents for cardiovascular use. It has been reported to cause sinus bradycardia, heart block, premature ventricular contractions, and ventricular tachycardia. Thrombosis has also been reported with the use of paclitaxel. In a large study of approximately 1000 patients, the incidence of cardiac toxicity was 14%, and most incidents (76%) were grade I asymptomatic bradycardia. Vinca alkaloids have been reported to cause autonomic neuropathy, Prinzmetal's angina with ECG changes and myocardial ischemia and infarction, reversible ECG changes has led to the hypothesis of ischemia induced by coronary spasm. Cardiac events are more likely to occur in women than in men[15].

The experience with anthracycline Cardiotoxicity proved that the early detection and treatment of Cardiotoxicity could significantly reduce the development of clinical manifestations. Endomyocardial biopsy is the most sensitive and specific way to diagnose and monitor anthracycline Cardiotoxicity, but the invasive nature of this procedure limits its use. The most common noninvasive method of monitoring myocardial toxicity from anthracyclines and other chemotherapeutic agents has been the assessment of LV systolic function, with echocardiography. Fractional shortening and LV ejection fraction are the most commonly used measurements, but both depend on preload and afterload. LV ejection fraction measurements also are not sensitive for the early detection of preclinical cardiac disease. Several studies have suggested that diastolic dysfunction is an early sign of anthracycline-induced cardiac dysfunction. Thus, measurements of diastolic function by Doppler echocardiography may be a sensitive method for early detection of toxicity. Provocative testing with exercise or Dobutamine echocardiography has also been used to assess early anthracycline Cardiotoxicity. Thus, these provocative-testing modalities may be sensitive for the early detection of subclinical cardiomyopathy and may provide an opportunity for therapeutic intervention before the development of overt LV dysfunction[16].

Biomarkers such as troponin I and T98 may be useful in early detection of doxorubicin Cardiotoxicity before the appearance of changes in LV ejection fraction, especially in children. During the past 10 years, several studies have confirmed the usefulness of B-type natriuretic peptide (BNP), a neurohormone elevated in response to volume overload, in the diagnosis and treatment of CHF. Recent studies in patients with neoplastic diseases have shown that high levels of BNP correlated with impairment of LV function during anthracycline therapy. BNP has also been shown to be elevated before the development of LV dysfunction in patients undergoing high-dose therapy and hematopoietic stem cell transplantation[17].

Monitoring for other anticancer drug–related cardiotoxic effects such as arrhythmias, ischemic cardiac events, and pericardial disease should be planned and specially tailored for each therapeutic protocol according to which anticancer agents are prescribed. Cardiac tests such as electrocardiography, rest and stress myocardial perfusion imaging, and troponin levels can be used to monitor ischemic cardiac complications. Echocardiography has emerged as the test of choice for the noninvasive evaluation of cardiac disease as related to cancer therapy. This tool is essential in the evaluation of LV systolic and diastolic function, pericardial disease, and detailed evaluation of valvular heart disease. Doppler echocardiography can also be used to assess hemodynamic status, including the presence of pulmonary hypertension. In patients with chemotherapy-induced cardiomyopathy, a decrease in BNP levels after dobutamine stress echocardiography correlated with the presence of contractile reserve. This finding also correlated with long-term improvement in LV systolic function and New York Heart Association class rating when patients were given beta-blockers and angiotensin converting enzyme (ACE) inhibitors[18].

Pre-chemotherapy workout:

A routine cardiologic consultation before initiating cardiotoxic chemotherapy is suggested, especially when using fluoropyrimidines or cisplatin based regimens. Dynamic investigations using stress tests (exercise ECG, dipyridamole-thallium scintigraphy, or dobutamine echocardiography) before the beginning of therapy may be important especially in high-risky patients. It is suggested a tight clinical monitoring of all patients receiving with agents reported to have been associated with acute coronary events. Patients should be immediately informed about the symptoms and the condition recognized and managed[19].

Strategies to Reduce Cardiovascular Toxicity and Manage Complications

Once cardiac toxicity is anticipated, strategies to control these adverse events can be developed, following are the few

Changing the dose and rate of administration:

Anthracycline toxicity can be minimized by reducing the total dose to >400 mg/m2 and changing the administration from a rapid infusion to a continuous infusion. Newer liposomal formulations also may reduce Cardiotoxicity[20].

Role of Dexrazoxane:-

Dexrazoxane is a derivative of EDTA, can reduce the amount of free iron in myocytes by producing free radicals that decrease oxidized iron levels during anthracycline infusion. Generally, Dexrazoxane has been recommended for patients with metastatic breast cancer who have received cumulative anthracycline doses of >300 mg/m2; Dexrazoxane is not recommended at the beginning of therapy because of the possibility of reducing the anticancer effect of the

anthracyclines. Dexrazoxane has led to improved survival in some studies, but whether this improvement was due to improved cardiac status is unclear. What is known, however, is that Dexrazoxane can worsen thrombocytopenia and granulocytopenia[21].

Avoiding combined administration:

The evolution of management strategies for trastuzumab related cardiac toxicity is following a progression similar to that of the anthracyclines. After initial reports that the combination of trastuzumab, anthracyclines, and cyclophosphamide led to severe heart failure in up to 16% of patients with breast cancer undergoing this treatment, the administration strategy was changed to avoid giving these drugs simultaneously, and more stringent cardiac monitoring was instituted. These modifications have considerably reduced toxicity rates[22].

Role of ACE inhibitors and Beta – blockers:

ACE inhibitors and beta-blockers are the cornerstones of therapy for LV dysfunction and should be administered to patients with cancer as aggressively as to any other patient population. This allows important anticancer therapy to be continued without compromising the patient's cardiac status[23].

Role of Statins:

Statins have shown to possess anti-inflammatory and anti-fibrotic properties and thought to interfere with and reduce the severity of anthracycline-induced cardiotoxicity. The mechanism by which statins are thought to reduce severity of anthracycline induced Cardiotoxicity include inhibition of production of reactive oxygen species and topoisomerase II inhibition[24].

Stopping the offending agent:

Much cardiac toxicity can be managed best by removing the offending agent. Unfortunately, in the case of newly developed LV dysfunction, chemotherapy may not be the only explanation for the reduced function, and thus all possible reversible causes should be investigated. In patients

With neoplastic disease , ischemia is still a reversible cause of LV dysfunction[25].

Conclusion:

The increased use of chemotherapy in modern medicine and cancer therapy has led to considerable number of patients presenting with chemotherapy induced cardiotoxicity. The patients who are successfully treated for malignancy may eventually land up in ICU due to cardiotoxicity. Management of such patients is important from the perspective of intensivists who need to be aware of such complications.

Conflict Of interest: None

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