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Case Report Open Access

Fatal Myocardial Infarction Secondary to Daunorubicin in Acute Myeloid Leukemia Patient

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Abstract

Acute myeloid leukemia is a type of cancer in which a myeloid stem cell, in the bone marrow, is altered or transformed. Myeloid stem cells give rise to red blood cells, platelets, and myeloblasts. When the bone marrow is replaced by leukemic cells, there is decreased production of the normal red blood cells, platelets, and white blood cells. This means both the bone marrow and blood are affected, leading to impaired delivery of oxygen and other substances in the body, decreased ability to fight infections and disease, as well as increased risk of bleeding secondary to the inability to create a platelet plug in blood clot formation. Symptoms include fatigue, shortness of breath, easy bruising and bleeding, and increased risk of infections. We present the case of a 46-year-old-woman with acute myeloid leukemia, M2 subtype with cytogenetic finding of inversion 16, whom underwent induction chemotherapy with daunorubicin. The patient's medical history included extensive cardiovascular disease, making the use of daunorubicin a precarious situation. Even with careful monitoring, the patient experienced a fatal myocardial infarction. This case highlights the use of daunorubicin, an FDA-approved drug for the treatment of acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) in adults, in a patient with pre-existing heart disease increasing the risk of daunorubicin-induced cardiac toxicity.

Keywords: Myocardial infarction; Daunorubicin; Anthracycline; AML

Text of Article

Acute myeloid leukemia (AML) is a cancer of a myeloid stem cell. There are different subtypes of AML. Treatment and prognosis vary accordingly. The median onset of age is 65 years. Laboratory testing usually initially shows an abnormal complete blood count with an overabundance of white blood cells being the most common sign. Increased circulating myeloblasts on peripheral smear provides a presumptive diagnosis, while definitive diagnosis requires bone marrow aspiration and biopsy. Risk factors include prior exposure to alkylating chemotherapy, radiation or myeloproliferative disorders. First-line treatment is chemotherapy, divided into 2 phases: induction and consolidation therapy. Anthracyclines are a group of highly potent chemotherapeutic agents that play a prominent role in the treatment of various forms of cancer [1]. These drugs have proven to be highly effective in the treatment of solid tumors, lymphomas, and leukemias, including AML [1]. Despite of their associated side effects, anthracyclines are extensively used for cancer therapy owing to their wide range of applications and high efficacy [1]. Hematopoietic stem cell transplantation can be considered if induction therapy is not successful in achieving complete remission or if relapse occurs.

The most commonly used anthracyclines for the treatment of AML are daunorubicin, doxorubicin, and idarubicin [2]. These drugs intercalate in the DNA, leading to breaks in the DNA and inhibition of biosynthesis and decreased replication. The most adverse side effect of anthracyclines is cumulative dose-related cardiotoxicity (dilated cardiomyopathy), which often limits the extent to which they can be used [3]. Several clinical factors increase the risk of the development of anthracycline-related cardiotoxicity, including: pre-existing cardiac disease, hypertension, hyperlipidemia, age >65 years, and previous radiation exposure [4].

The mechanism of anthracycline-induced cardiotoxicity remains unclear, however, it is believed to be multifactorial. The most widely accepted hypothesis suggests that anthracyclines interfere with redox cycling leading to the production of reactive oxygen species, leading to DNA damage [5]. Recently, it has also been suggested that topoisomerase-2 may be the main mediator of anthracycline-related cardiotoxicity [5].

Anthracycline-related cardiotoxicity manifests as a broad range of cardiac malfunction. These include severe overt cardiac symptoms requiring immediate medical care (incidence 2-4%), asymptomatic cardiac structural changes detectable on imaging (incidence 9-11%), new onset arrhythmia (incidence >12%), or the rise in biomarkers prior to the onset of detectable cardiac changes (incidence 30-35%) [5]. The most important form of cardiotoxicity is dilated cardiomyopathy, which can lead to congestive heart failure and even death [3]. In most cases, dilated cardiomyopathy occurs within one year of initiation of anthracycline therapy. In addition to dilated cardiomyopathy, sub-clinical structural changes in the form of left ventricular systolic dysfunction and arrhythmias such as atrial fibrillation have also been observed in several cases [5].

An early biomarker of daunorubicin-induced cardiotoxicity is troponin. A rise in troponin is seen after initiation of anthracycline therapy in 21-40% of the patients [5]. The level of troponin is directly proportional to the amount cardiac damage. Troponin is an intracellular enzyme only detectable in the blood when cells have lysed

and expulsed their contents. In the setting of anthracycline-cardiotoxicity, a rise in troponin may indicate cardiomyocyte apoptosis as well as myofibril degradation [5].

Anthracyclines improve cancer outcomes and survival rates, as well as concomitantly increasing cardiovascular morbidity and mortality. In cancer survivors, the long term cardiovascular outcomes vary depending on the patient risk profile. The predictors for cardiovascular outcomes in adults include patient age, anthracycline dosage, time since chemotherapy, and chest radiotherapy [5].

Case Report

A 46-year-old woman presented for treatment of AML, of the M2 subtype with cytogenetic findings of inversion 16. This cytogenetic finding placed her disease in the favourable risk category to achieve a complete remission. The patient's past medical history was significant for complex coronary artery disease (CAD), hyperlipidemia (HLD), diabetes mellitus type 2, peripheral vascular disease, cerebrovascular accident, chronic obstructive pulmonary disorder, and hypertension (HTN). Surgical history included three coronary artery bypass grafts, multiple stent placements, right carotid endarterectomy, femoral endarterectomy and appendectomy. At the time of diagnosis, the patient's bone marrow aspiration and biopsy showed adequate iron stores and the presence of 45% blast cells with no ringed sideroblasts. A pre-treatment echocardiogram showed normal global left ventricular systolic function, with a visually estimated ejection fraction (EF) of 50-55%.

The benefit-to-risk ratio of therapy was weighed before she completed induction chemotherapy with daunorubicin (60 mg/m^2) and cytarabine (200 mg/m^2). Following induction, subsequent bone marrow aspiration and biopsy revealed hypocellular regenerating bone marrow with no evidence of residual leukemia and increased (3+) iron stores. An echocardiogram at this time revealed mildly reduced global left ventricular systolic function, with a visually estimated EF of 45-50%. Right ventricular systolic function appeared normal. The right ventricle and left atrium appeared enlarged. Moderate mitral regurgitation and mild tricuspid regurgitation were present. Doppler studies suggested severely elevated right-sided pressures.

A few days later the patient was hospitalized status post a mechanical fall at home. During this admission, she developed a pulmonary embolus (PE), deep venous thrombosis and recurrent non-ST elevation myocardial infarction (NSTEMI). She was referred for cardiac catheterization after discussion with the multiple teams involved, as well as the patient and her husband regarding the risks and benefits of the procedure. After receiving four units of packed red blood cells she underwent catheterization. This showed severe 3-vessel coronary artery disease, patent left internal mammary artery to the left anterior descending, patient saphenous venous graft to the third obtuse marginal branch with 95% ostial stenosis, and 70% left main stenosis going into the proximal part of the circumflex vessel. Successful balloon angioplasty and bare metal stenting of 95% hazy stenosis in the ostium of the saphenous venous graft to the third obtuse marginal branch. Post-op recovery was unremarkable. Aspirin and statin therapy was recommended for life along with clopidogrel therapy for a minimum of one month after bare metal stenting, preferably longer given acute myocardial infarction presentation.

Because of the PE and NSTEMI, the planned consolidation treatment was slightly postponed. Before beginning the first consolidation treatment cycle, the patient had another echocardiogram and bone marrow aspiration. The echocardiogram revealed further reduced left ventricular systolic function, the EF now visually estimated to be 35-40%, regional wall motion abnormalities, grade 2 moderate diastolic dysfunction, normal right ventricular systolic function, enlarged right ventricle, moderate mitral and tricuspid regurgitation, and Doppler studies suggesting moderately elevated right sided pressures. The bone marrow aspiration revealed normocellular marrow, no evidence of residual leukemia, adequate 2+ iron stores, and no ringed sideroblasts. No abnormalities were detected by flow cytometry.

Thereafter, the patient received the first cycle of consolidation therapy with high dose cytarabine (1500 mg/m^2 intravenously). The patient tolerated the treatment regimen well and had no major complications. She did experience one episode of multiple premature ventricular contractions and associated chest discomfort. The patient was then discharged to be followed on an outpatient basis.

A few weeks later, the patient was admitted for platelet and packed red blood cell transfusion secondary to anemia and low platelet count, sequelae of her AML and its treatment. After one unit of platelet transfusion, she developed sudden-onset respiratory failure along with cardiac arrest. She received cardiopulmonary resuscitation for five minutes before an airway was established. After definitive airway management, large volumes of pink colored fluid were drained from her lungs. She was resuscitated and placed on a mechanical ventilator and vasopressors. Bronchoscopy revealed large volumes of alveolar hemorrhage in the lungs. It was then noted during routine physical examination, that pulses were not palpable in her lower extremities; this was likely due to vasospasm secondary to norepinephrine usage in a setting in which the patient had a known history of chronic complex arterial disease. The femoral pulses were able to auscultated via Doppler bilaterally, whereas, the dorsalis pedis and posterior tibial pulses were not.

Subsequently, the patient developed oliguria. Nephrology was consulted and she was placed on continuous veno-venous hemofiltration. Overnight, the patient developed severe metabolic acidosis and disseminated intravascular coagulation. The patient's troponin levels, which were previously repeatedly at a level of 0.3, increased to 9.26.

As the patient's condition deteriorated, palliative care was consulted and a meeting with the family was arranged. It was unanimously decided to transition to comfort care measures, shortly after which the patient died. The patient's family wished for an autopsy following a discussion with the attending physician about the patient's hospital course, management and possible etiology of her condition.

The autopsy report included the primary diagnoses of: cardiac arrest, acute respiratory failure, AML-M2, pancytopenia secondary to AML, CAD status post coronary artery bypass graft and placement of multiple stents, ischemic cardiomyopathy, and severe metabolic and respiratory acidosis. Secondary Diagnoses included: insulin-dependent diabetes mellitus, peripheral vascular disease, and chronic obstructive pulmonary disease. Main autopsy findings include: acute myocardial infarction, congestive heart failure with cardiomegaly, left and right ventricular hypertrophy, and calcified aortic valve, severe pulmonary edema and congestion, acute and chronic congestion of liver and spleen, and bilateral chronic pyelonephritis and acute tubular necrosis. The minor autopsy finding was bilateral xanthelasma on the eyelids.

Discussions and Comments

The survival of cancer patients after chemotherapeutic treatment has markedly increased in the last decade [6]. Anthracyclines play a key role in most chemotherapeutic drug regimens. However, adverse effects of aggressive anthracycline chemotherapy also exist [6]. Adverse cardiac effects are some of the deadliest side effects increasing the morbidity and mortality rates. Cardiotoxic chemotherapeutic agents such as daunorubicin can decrease myocardial contractility and cardiac functioning. Such cardiotoxic effects can manifest at variable time frames following chemotherapy [6]. Additionally, anthracyclines have been shown to decrease endothelial cell protein C receptor in a time and dose dependent manner. This results in a decrease in activation of protein C and may contribute to the thrombogenic mechanism of some chemotherapeutic regimens [7].

The above case study is a typical example of anthracycline-induced cardiotoxicity and thrombogenesis during treatment of AML. It also demonstrates another potential side effect of anthracycline therapy: acute myocardial infarction. The patient received induction chemotherapy with the standard 7+3 regimen anthracycline base of daunorubicin and cytarabine because it is the most effective current therapy to provide a cure. Given that the patient had favourable risk AML cytogenetic findings, obtaining a complete remission and completing consolidation would have provided her the best chance for long term survival. Selection of an alternative therapy would have significantly decreased the likelihood of complete remission and thus long term survival. With the knowledge that the patient was high risk for cardiac-related issues regarding the use of anthracycline, this was discussed with the patient and her family who elected to pursue the 7+3 regimen even with the increased risk of cardiac complications, given that this regimen provided the highest chance of cure.

The anthracycline was given on days 1-3 per treatment regimen. Total dose was 180 mg/m^2, yet the patient still suffered an NSTEMI. This is likely due to the patient's high clinical risk pre-treatment. In accordance with the patient's high-risk profile, the development of daunorubicin cardiotoxicity commenced soon after induction chemotherapy. There is no reliable method of predicting in whom cardiac side effects will develop as a result of the cardiac toxic effect of daunorubicin. However, certain changes in the electrocardiogram and a decrease in systolic ejection fraction from pre-treatment baseline may help to recognize these patients at greatest risk. This was evidenced in our patient's serial echocardiographic findings, as abnormalities in flow and function continued to develop. In the event that this predictive parameter shows declining cardiac function, the benefit of continued therapy must be weighed against the risk of producing further cardiac damage. The most notable echocardiography abnormality consistent with daunorubicin toxicity is reduction of left ventricular systolic function with a fall in the EF of >10%. Furthermore, in addition to the patient's echocardiography findings, the rise in the cardiac biomarker troponin may be an indication of daunorubicin cardiotoxicity. We recognize the rise in troponin, a marker of cardiac ischemia, after receiving cardiopulmonary resuscitation is inevitable.

Conclusion

Anthracycline-induced cardiotoxicity is a major obstacle of anthracycline chemotherapy. Several potential cardio-protective strategies have been explored to minimize anthracycline related cardiotoxicity [8]. The most important implementations include limiting the drug dosage, modification of anthracycline structure to create modified analogues of the drug that are comparably less cardiotoxic, liposomal encapsulation, and concurrent administration of iron chelators [1]. Perhaps in this case, a lower dose of anthracycline (45 mg/m^2 instead of 60 mg/m^2) could have been used, but this would have affected the efficacy. It is essential to conduct research to investigate novel techniques and drugs that can be used to combat anthracycline cardiotoxicity to allow for effective treatment of cancer in the face of pre-existing cardiac and vascular disease which is ever prominent. If new agents are proven effective in treating AML which are not cardiotoxic, it would be ideal for this case presentation. The importance of ongoing research into effective AML induction regimens which are less toxic remains of vital importance.

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