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Hemodynamic Instability and Acute Pulmonary Toxicity to Azacitidine in a Patient with Acute Myelogenous Leukemia

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Abstract

Azacitidine, a deoxyribonucleic acid (DNA) hypomethylating agent, is an increasingly utilized treatment option for elderly patients with acute myeloid leukemia (AML), who are not considered candidates for intensive chemotherapy. Mild adverse reactions to azacitidine, both hematologic and non-hematologic are not uncommon, but severe adverse effects are rare. The most commonly reported toxicities are myelosuppression, gastrointestinal distress, and pain at the injection site.

We describe a 77-year-old man with newly diagnosed AML, who was treated with subcutaneous azacitidine, and experienced severe life-threatening side effects with the first dose that recurred upon administration of a second dose. Following administration of each dose, the patient developed hyperthermia, severe hypertension followed by hypotension, requiring vasopressor support and hypoxic respiratory failure. No other attributable causes, including infectious etiologies, were identified. Clinicians should be aware of this rare, life-threatening adverse effect of azacitidine.

Keywords

Acute myelogenous leukemia; Azacitidine; Pneumonitis; Drug toxicity

Abbreviations

DNA: Deoxyribonucleic acid; AML: Acute myeloid leukemia; OS: Overall Survival; RBC: Red blood cell; BM: Bone marrow; AIDS: Acquired Immunodeficiency Syndrome; β: Beta; MDS: Myelodysplastic Syndromes; g/dL: grams of hemoglobin per deciliter; L or l: Liter; FISH: Fluorescent in situ hybridization; RUNX1T1: Runt related transcription factor 1; translocated to, 1 (cyclin D related); RUNX1: Runt related transcription factor 1; KMT2A: Lysine (K)-specific methyltransferase 2A; Mg: Milligram; m^2: Square meter; °F: Fahrenheit; mmHg: millimeter of mercury; BPM: Beats per minute; ANC: Absolute neutrophil count; ICU: Intensive care unit; EF: Ejection fraction; IV: Intravenous; BiPAP: Bilevel Positive Airway Pressure; TACO: transfusion associated circulatory overload; TRALI: transfusion related acute lung injury; ALI: Acute lung injury; HLA: Human leukocyte antigen; HNA: Human neutrophil antigen-3

Introduction

Acute myeloid leukemia (AML) is associated with a poor prognosis in elderly patients. Overall survival (OS) in this patient population is dismal with the 2- and 5-year overall survival rates reported to be 10% and 2%, respectively [1]. Intensive chemotherapy is generally not administered due to poor

patient performance status, significant co-morbidities, and poor treatment tolerance [2].

Azacitidine has been increasingly used to treat elderly patients with AML. A phase III international multicenter randomized controlled trial comparing azacitidine to conventional care showed azacitidine to be well-tolerated and superior in prolonging overall survival [3]. Many patients achieved red blood cell (RBC) transfusion independence in response to azacitidine, and the number of days in-hospital compared to conventional care were significantly reduced in older adult patients with World Health Organization defined AML with bone marrow (BM) blast counts of 20% to 30%.

Azacitidine is a DNA hypomethylating agent that has been studied in a wide variety of diseases including; acquired immunodeficiency syndrome (AIDS), β-thalassemia, sickle cell disease, melanoma, metastatic lung cancer, hormone-refractory prostate cancer, cancer of the cervix, ovaries, colon, rectum, and head and neck [4-8]. Azacitidine has shown the greatest activity in treatment of patients with AML and myelodysplastic syndromes (MDS) [3,9]. It is currently a standard of care treatment option for patients with high-risk MDS and AML, who are not candidates for high-dose chemotherapy and hematopoietic cell transplantation.

Azacitidine is generally well-tolerated, and can be administered in an outpatient setting; however, there is the potential for mild adverse reactions. Nausea, vomiting, constipation, diarrhea, fever, fatigue, mucositis, and local injection site reactions have all been reported. Severe adverse reactions are extremely uncommon [10].

We report here, a 77-year-old Caucasian man with newly diagnosed AML who developed life-threatening hypoxia, hyperthermia, and hypotension within hours after receiving his first dose of azacitidine that recurred following a second dose of azacitidine and could not be attributed to other identifiable causes.

Case Report

A 77-year-old male was referred by his primary care physician to our cancer institute for evaluation of progressive pancytopenia, easy bruising, mild epistaxis, and fatigue. His past medical history was significant for type 2 diabetes mellitus, hypertension, dyslipidemia, and chronic kidney disease. Labs at presentation showed a white blood cell count of 2.3 x$10^{3/}$l, hemoglobin of 6.6 g/dL, and a platelet count of 3.7 x 10^{3}/l. His peripheral blood smear showed a myeloid left shift with 11% blasts. A bone marrow biopsy was hypercellular with greater than 90% cellularity and 88% blasts. An AML fluorescent in situ hybridization (FISH) panel revealed 4 copies of all probes tested (5,7q,8,20q,20 , RUNX1T1 ,RUNX1, and KMT2A) consistent with a tetraploid karyotype.

Treatment with azacitidine at a standard dose of 75mg/m^{2}/day subcutaneously was initiated in the outpatient infusion center. Following the first dose, the patient returned home, but within one hour developed nausea, vomiting, and a fever of 104.2°F. He was transported to the local emergency room, where he was found to be febrile to 103°F, hypotensive with a blood pressure of 100/50 mmHg, and tachycardic with a pulse of 137 beats per minute (bpm). He was also noted to be hypoxemic on room air with an oxygen saturation of 87%. Labs were remarkable for a hemoglobin of 7.3 g/dL, a platelet count of 7 x 10^{3}/l, and absolute neutrophil count (ANC) of 1.56 x$10^{3/}$l. A chest X-ray showed a normal heart size and clear lungs fields (Figure A).

The patient was placed on supplemental oxygen (2L) by nasal cannula, given intravenous fluids, transfused platelets, and transported by squad to our hospital, where he was admitted to the intensive care unit (ICU). He was begun on broad-spectrum intravenous antimicrobials and aggressively resuscitated with intravenous fluids, red blood cell and platelet transfusions. Due to refractory hypotension, vasopressors were initiated. He experienced progressive tachypnea and hypoxemia, and was switched to oxygen supplementation by vapotherm. A repeat chest X-ray (FigureB) showed diffuse hazy interstitial opacities and a CT scan of the thorax revealed bilateral upper lobe ground glass opacities, patchy pneumonitis and mild to moderate interstitial fibrosis with trace bilateral pleural effusions (Figure C and D). A transthoracic echocardiogram showed left ventricular hypertrophy, with an ejection fraction (EF) of 55% and moderate pulmonary hypertension.

The patient's blood pressure stabilized permitting discontinuation of vasopressors. He was subsequently given intravenous (IV) diuretics with significant clinical improvement within 24 hours. He was weaned off oxygen and pressors entirely. Blood cultures and a viral respiratory panel were negative; hence, antimicrobials were discontinued and he was transferred to a floor bed. A repeat chest X-ray showed complete resolution of the interstitial abnormalities noted on the film obtained 48 hours earlier (Figure E).

The patient returned to his baseline state remaining on room air, afebrile, with a stable blood pressure and normal heart rate. Due to the rapid onset of the patient's symptoms in relationship to his first dose of azacitidine, and concerns his symptoms were due to an adverse reactionto azacitidine, the decision was made to administer the patient's second dose of azacitidine in the hospital under close observation. A second dose of azacitidine 75mg/m^2 subcutaneously was administered,96 hours after the initial dose. Notably, within one hour after receiving dose 2 of azacitidine, the patient again developed nausea and vomiting, followed by tachycardia with a pulse rate exceeding 150 bpm, fever to 103°F, hypertension with a blood pressure of 160/110 mmHg, then hypotension with a systolic blood pressure of 80 mmHg, and hypoxia. The patient was given intravenous crystalloid fluid resuscitation, vasopressors, and supplemental oxygen. He was pan-cultured and restarted on empiric broad spectrum intravenous antibiotics. He remained febrile over the ensuing eight hours despite treatment with acetaminophen. Glucocorticoids were eventually required, and followed by significant improvement in his hemodynamics. His infectious work-up again proved to be negative.

The patient's subsequent clinical course was complicated by oliguric acute kidney injury leading to volume overload and hypoxia, requiring non-invasive mechanical ventilation with Bilevel Positive Airway Pressure (BiPAP). Given the patient's worsening renal function with uremia and continued hypoxia, a family meeting was held and the patient was transitioned to hospice care per the patient's and family's request.

Discussion

Azacitidine, a cytidine analog with hypomethylating activity, is approved for the treatment of myelodysplasia (MDS) and AML [3,9,10]. It is a preferred agent for the treatment of AML in the elderly and in those with significant comorbidities due to its safety profile. The most common toxicities reported are worsening cytopenias and myelosuppression.

Rare non-hematologic adverse effects have been reported with azacitidine including acute

interstitial pneumonitis [11-15], acute myocarditis [16], hypersensitivity pneumonitis, and Sweet's syndrome [17]. Here we describe a life-threatening adverse reaction to azacitidine that has not previously been reported in the published literature, consisting of a constellation of fever, hypoxic respiratory failure, and autonomic instability requiring vasopressor support. Re-challenging the patient with a second dose of azacitidine, following his recovery from the first dose precipitated the identical life threatening adverse reaction, requiring discontinuation of azacitidine.

As clinicians, it is important to consider other entities in the differential diagnosis. Clinical conditions such as aspiration pneumonitis, sepsis, trauma, pulmonary contusion, burn injuries or shock can also precipitate acute lung injury. Our patient suffered from none of these. A similar picture could also result from transfusion associated circulatory overload (TACO) or possible transfusion related acute lung injury (TRALI) [18-21].

TRALI is defined as a new episode of acute lung injury occurring during or within 6 hours of a completed transfusion that results from donor leukocyte antibodies and recipient neutrophil sequestration and activation leading to endothelial injury and increased pulmonary vascular permeability. The symptoms of TRALI include dyspnea, fever, hypotension, tachypnea, and tachycardia. Mechanical ventilation may be required to support oxygenation. TRALI is a clinical and radiographic diagnosis; it is a clinical syndrome rather than a disease with a single etiology. A diagnosis of TRALI should be considered as a cause of acute lung injury based on its time of onset in relationship to a transfusion, the presence of hypoxemia, chest radiograph abnormalities, and the absence of evidence of circulatory overload, caused either by transfusion or by preexisting cardiac conditions. When the acute insult is temporally related to both transfusion and at least one other risk factor, it is known as “possible TRALI.” The distinction between TRALI and possible TRALI is subjective, requiring further clinical assessment and proper documentation including the time course of symptom evolution and alternate risk factors for acute lung injury as mentioned above. Whenever TRALI or possible TRALI is suspected, clinicians should obtain a recipient blood specimen for typing HLA Class I and Class II antigens, and for neutrophil antigens as well. Similarly, the donor blood specimens should be tested for HLA Class I, HLA Class II, and neutrophilantigen and antibodies.

Patients with TACO develop symptoms within hours of a transfusion, and may also present with acute elevations in blood pressure, widened pulse pressure, tachycardia, and other signs of volume overload. Increased intravascular volume and elevated hydrostatic pressure exceeding the physiologic capacity of the cardiovascular system leads to pulmonary edema in patients with TACO, which can be particularly problematic in elderly patients prone to mild diastolic dysfunction.

It is notable that our patient did not receive any transfusions prior to the onset of his symptoms, ruling out a diagnosis of TACO or TRALI. The acute onset of his symptoms was temporally related to the administration of azacitidine. The patient developed symptoms within one hour following administration of the first dose of azacitidine. His symptoms recurred one hour after the second dose, which was administered days later, after he had recovered from the first dose. These observations provide strong support that a severe adverse reaction to azacitidine was the initiating event in the pathogenesis of our patient's clinical deterioration.

The pathogenesis of antineoplastic agent-induced lung injury remains poorly understood. Most

toxic effects are thought to result from direct cytotoxicity. The pathophysiologic mechanisms that have been proposed include direct injury to pneumocytes or the alveolar capillary endothelium with the subsequent release of cytokines, resulting in endothelial dysfunction, capillary leak syndrome, and non-cardiogenic pulmonary edema. Activation of lymphocytes and alveolar macrophages can also lead to cell-mediated lung injury. Oxidative injury from the generation of free oxygen radicals may add to the acute insult [22].

Although we do not know the exact mechanism of the lung injury induced by azacitidine, we suspect it was due to a direct cytotoxic effect with damage to capillary endothelial cells causing leakage of fluid and pulmonary edema. It is possible that an allergic or hypersensitivity reaction may have also contributed [11-15].

Conclusion

In conclusion, we report a case of a life-threatening adverse reaction to azacitidine characterized by acute respiratory failure with interstitial pneumonitis [12] autonomic instability with initial grade 2 hypertension followed by severe hypotension requiring vasopressor support, and concomitant hyperthermia. A thorough workup failed to reveal an infectious etiology for either the hyperthermia or severe hypotension. Clinicians should be aware of this rare, life-threatening, adverse effect of azacitidine.

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Figures

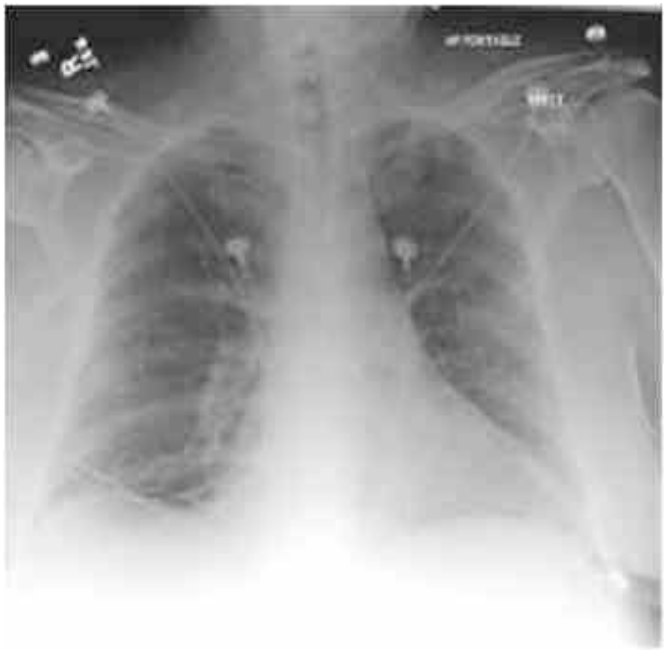


Figure A: Initial Chest X-ray

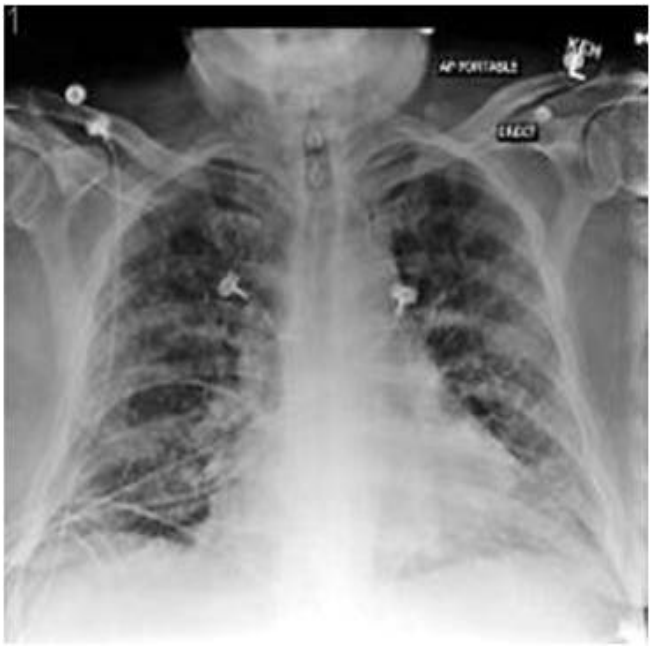
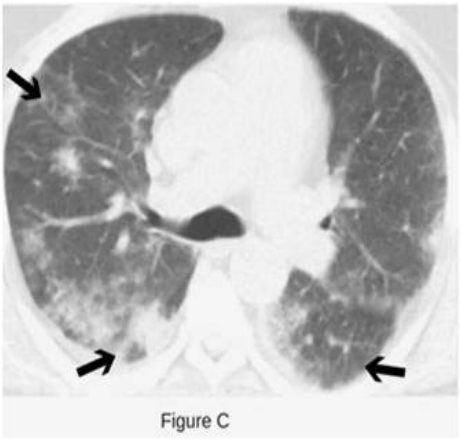


Figure B: Subsequent Chest X-ray with progressive hypoxia



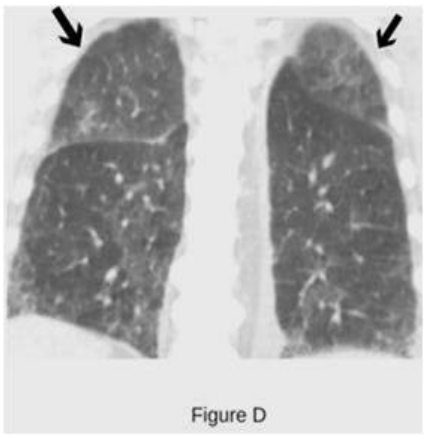


Figure C&D: Chest computed tomography scan revealing bilateral upper lobe ground glass opacities (*arrow heads*) and mild to moderate interstitial fibrosis.

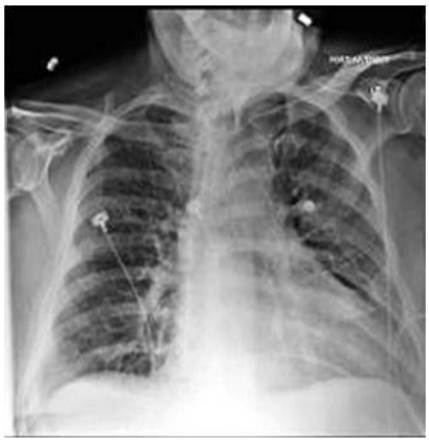


Figure E: Follow up chest x-ray

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