Case Report

Complete heart block in a neutropenic patient with aspergillosis: An unusual adverse effect of caspofungins

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ABSTRACT

We present a case of complete heart block (CHB) in a 58-year-old female patient with acute myeloid leukemia (AML) with no past history of cardiac disease, who received caspofungin in the treatment of disseminated fungal infection. To our knowledge, this is the first case of CHB associated with caspofungins. Subsequent to induction chemotherapy the patient developed invasive pulmonary aspergillosis with sudden tachypnea, dyspnoea, fever, bilateral pulmonary infiltrates and acute respiratory insufficiency consequent to neutropenia with ANC<500. During the first dose of antifungal therapy with caspofungins, she developed complete atrioventricular block and cardiac arrest. Complete heart block is an unusual adverse effect of caspofungins which has not been reported previously. Caspofungins release histamine in peripheral blood cells, so possible histamine-mediated symptoms ranging from severe fatal anaphylaxis can occur. These data suggest that infusion-related reactions associated with caspofungin may be mediated by histamine release secondary to caspofungin therapy.

Key words: Acute myeloid leukemia, complete heart block, caspofungins, pulmonary aspergillosis

INTRODUCTION

Acute myeloid leukemia a cancer of the blood and bone marrow is the most common type of acute leukemia in adults which usually quickly gets worse if not treated. The treatment of AML varies according to one's age, general condition at diagnosis, and cytogenetic parameters. Diagnosis is made when blood and bone marrow samples show a large number of leukemia cells. AML is further subdivided into eight subtypes, labeled M0 to M7, basing on the type of blood cells affected, by the method of flow cytometry. For most patients aged 69 or younger, the first line treatment consists primarily of chemotherapy, which is usually divided into two phases: Induction and post remission (or consolidation) therapy. The goal of induction therapy is to achieve a complete remission by reducing the amount of leukemic cells to an undetectable level where as the goal of consolidation therapy is to eliminate any residual undetectable disease and achieve a complete cure.

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Induction therapy for such patients (except the M3 subtype), under the age of 70 typically includes cytarabine (ara-C), an anthracycline (such as daunorubicin or idarubicin and occasionally etoposide chemotherapy. These medications are given over a six- to seven-day period, followed by three or more weeks of recovery period, for the patient to recover from the treatment. This induction chemotherapy regimen is known as "7+3" (or "3+7"), because the cytarabine is given as a continuous

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IV infusion for seven consecutive days while the anthracycline drug is given for three consecutive days also intravenously. Up to 70% of patients usually achieve a remission with this protocol.[1]

Invasive fungal infections (IFI) due to Aspergillus, Fusarium, and Mucorales species, and Pneumocystis jirovecii infections are a frequent complication of neutropenia due to such intensive chemotherapy for acute leukemias. Out of these IFI, invasive aspergilosis (IA) is a significant cause of life-threatening infection in severely immunocompromised patients, especially those with AML.[2] Several challenges exist in the treatment of such IFIs because early and correct diagnosis of such fungal infections is usually difficult as these saprophytic fungi are usually resistant to the conventional drugs, and hence monotherapy with antifungal agents is often unsuccessful. All these results in increased mortality which is higher in older patients. The "gold standard" treatment for IFIs has been the use of either amphotericin B deoxycholate or lipid formulations of amphotericin B. However, certain studies indicate that invasive aspergillosis do not respond well to amphotericin B, even when lipid formulations are used.[3]

However the therapeutic strategy of aspergillosis has been totally modified with the emergence of echinocandins. The echinocandins are a class of intravenous antifungal agents that represents a promising advancement in the treatment of invasive fungal infections due to the Candida and Aspergillus species. Currently, two echinocandin antifungal agents, micafungin (Mycamine) and caspofungin (Cancidas) are approved by the Food and Drug Administration (FDA) which have documented activity against invasive candidiasis and refractory Aspergillus. Cancidas (caspofungin acetate) is a sterile, lyophilized product for intravenous infusion that contains a semisynthetic lipopeptide (echinocandin) compound synthesized from a fermentation product of Glarea lozoyensis. It is indicated in empirical therapy for presumed fungal infections in febrile, neutropenic adults and pediatric patients (3 months and older) and in those who are refractory to or intolerant to other antifungal therapies.[4] Thus caspofungins have the advantages of a broad spectrum of activity, favorable tolerability profile, with no hepatotoxic or nephrotoxic adverse effects. With the event of the ongoing post marketing surveillance with this drug, till date the adverse effects reported with these novel wonder drugs are generally of low grade. But here we report a new unreported side effect of caspofungin in a patient of AML with no past history of cardiac disease, who developed complete heart block, during treatment with cansidas for pulmonary aspergillosis.

CASE REPORT

We report the case of a 58-year-old female who was admitted to the Medicine Department of S.C.B Medical College and Hospital, Cuttack in june 2010 because of generalized lymphadenopathy and vomiting. Her peripheral blood smear showed leukocytosis with a WBC of 93,500/microliters, and the bone marrow picture revealed a predominance of blast cells. The blasts were negative for peroxidase, alpha-naphthyl butyrate esterase and PAS. A diagnosis of AML, M0 was made, based on the FAB criteria. She was treated with 3+7 induction therapy, where daunorubicin was given in a dose of 60mg/m$^{[2]}$/day for 3 days and cytarabine in a dose of 100 mg/ m$^{[2]}$/day for 7 days. Post induction remission chemotherapy bone marrow evaluation confirmed the achievement of complete haematological remission. Subsequently she received high dose cytosine arabinoside in a dose of 3 gm/m$^{[2]}$/dose. After 9 days of this high dose chemotherapy she developed mucosal toxicities and high fever with cough during the hospital course. This febrile episode was associated with neutropenia with absolute neutrophil count 500 mm$^{[3]}$. So empirical antimicrobial therapy with cefepime and amikacin was started. Although there was a slight decrease in her temperature and moderate improvement in her general condition, she developed sudden tachypnea, dyspnea, fever, bilateral pulmonary infiltrates and acute respiratory distress on the sixteenth day for which she had to be put in a ventillator. Blood, urine and nasopharyngeal swab cultures were negative. Radiological investigations revealed the presence of bilateral consolidations. Pulmonary CT scan was performed which showed bilateral diffuse pulmonary infiltrations suggesting fungal or bacterial pneumonia. There was also no sign of pericardial involvement. Diagnosis of invasive pulmonary aspergillosis (IPA) was done on the basis of isolation of an Aspergillus species from the sputum and from bronchoalveolar lavage samples. The admission electrocardiogram (ECG) had revealed normal sinus rhythm. Basing on the laboratory diagnosis she was administered a single loading dose of 70-mg of caspofungin as intravenous infusion over a period of 1 h. But 45 minutes after the start of the infusion, She developed bradycardia and hypotension which did not respond to frequent fluid boluses. The ECG showed complete atrioventricular (AV) block. In spite of cardiopulmonary resuscitation, the patient died of complete AV block on the same day.

DISCUSSIONS

Invasive aspergillosis is a frequently encountered infection in AML patients undergoing induction chemotherapy due to prolonged and profound neutropenia as a sequel of chemotherapy where antifungal therapy remains the main stay of treatment. Cardiac involvement by aspergillus is though rare, may result from contagious spread from the lungs or from hematogenous spread. Pericardial and myocardial aspergillosis are rare manifestations of systemic aspergillosis which can result in arrhythmias and death.[5]

Caspofungin are generally well tolerated drugs for drug-related adverse events reported till date is not considered serious. Infusion-related adverse events though reported in 2 patients (5.1%) were judged to be mild in intensity.[4] Caspofungins release histamine in peripheral blood cells, so possible histamine-mediated symptoms ranging from severe fatal anaphylaxis to milder side effects like rashes, facial swelling, pruritus, sensation of warmth, or bronchospasm have been reported. Reported cardiovascular side effects with caspofungins include hypotension (up to 20%), tachycardia (up to 8%), hypertension (up to 6%) and arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, myocardial infarction (in less than 5%).

We also searched the literature about cardiac side effects of caspofungins but such acute cardiac events have not been reported during the first dose of cancidas infusion. A study created by eHealth Me based on 37 reports from FDA and user community reports that caspofungins can cause heart attack in less than 2%, coronary artery disease in 0.05% of people. On Oct, 8, 2011: 1,906 people reported to have side effects when taking Cancidas. Among them, 37 people (1.94%) had cardiac arrest out of which 71.43% were males in comparision to 28.57% who were females.[6] 29.79% of the people who had cardiac arrest with caspofungins were more than 60 yrs of age. The top conditions associated with these people were aspergillosis, candida sepsis, fungal infection, atrial flutter, septicaemia. The reasons behind these dysrthymias are unclear. It is postulated that histamine released by caspofungins caused the AV block in our patient. Though histamine release is a common feature of such infusion related side effects, however cardiac arrest due to hypokalemia which is a very rare side effect (23.4 % with amphotericin as compared to 9.9 % with caspofungins) cannot be ruled out.[7]

Since permission for a postmortem examination was not provided by the family, we were unable to show possible cardiac fungal involvement that could be responsible for the complete heart block in our patient.

CONCLUSION

Caspofungins as antifungal therapies for disseminated fungal infections are being increasingly used, although the safety of these regimens has never been established. Clinicians should be cognizant that CHB is a potential side effect of caspofungin for the treatment of disseminated fungal infections.

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