Fludarabine-induced bradycardia in a patient with refractory leukemia

To the Editor: A 22-year-old male diagnosed with acute myelogenous leukemia in November 2005 achieved complete remission after two courses of induction chemotherapy with idarubicin (12 mg/m² intravenously for 3 days) and cytosine arabinoside (200 mg/m² in a 24-hour infusion for 7 days). He then received an additional two courses of cytosine arabinoside (3000 mg/m²) in a 3-hour continuous intravenous infusion twice daily for 3 days in April 2006 for intensification. Six months later, the leukemia relapsed and was refractory to re-induction chemotherapy (idarubicin 12 mg/m² on days 1-3 and cytosine arabinoside 200 mg/m² on days 1-7). With the exception of myelosuppression, no toxic events occurred during idarubicin and cytosine arabinoside treatment. Due to the refractoriness to re-induction chemotherapy, salvage chemotherapy with the FLAGI regimen (fludarabine 30 mg/m² on days 1-5, cytosine arabinoside 2000 mg/m² on days 1-5, and idarubicin 12 mg/m² on days 7-8) was prescribed. Before chemotherapy, his vital signs were stable, with a blood pressure of 111/65 mm Hg, a respiratory rate of 19/min, a heart rate of 97/min, and a body temperature of 36.6°C. An electrocardiogram (ECG) showed a normal sinus rhythm (Figure 1a). Premedication included dexamethasone, granisetron, and metoclopramide, which were prescribed in previous chemotherapy. Thirty minutes after the fludarabine infusion had been started, he developed sudden-onset general weakness, which lessened 5 minutes later. At that time, persistent bradycardia (48 beats per minute) was noted; vital signs were otherwise normal (blood pressure, 120/70 mm Hg; respiratory rate, 20/min; and body temperature, 36.1°C). ECG revealed sinus bradycardia but no atrioventricular block, ST segment elevation or depression, or T wave inversion (Figure 1b). The patient did not have chest tightness or pain, dizziness, cold sweats, palpitations, dyspnea, or fever with chills. Investigations showed serum potassium 4.9 mmol/L (normal, 3.5-4.5 mmol/L), creatinine 1.0 gm/dL (normal, 0.5-1.3 g/dL), CPK 19 IU/L (normal, 38-174 IU/L), creatine kinase MB fraction 2.7 U/L (normal, 3-10 U/L), and troponin I < 0.04 ng/ml (normal, <0.8 ng/ml). No specific therapy was administered; however, oxygen was given at 4 L/min via nasal cannula. The persistent bradycardia resolved gradually, 3 hours after cessation of the 5-day fludarabine infusion (Figure 1c); he then received 2 days of idarubicin treatment without incident (Figure 2).

Cytosine arabinoside is frequently used in the treatment of hematologic malignancies, especially acute myelogenous leukemia. Sporadic cases of pericarditis, peri-
cardial effusion, cardiac tamponade, congestive heart failure, and sinus bradycardia have previously been reported as complications of cytosine arabinoside.\textsuperscript{1,3} Fludarabine is a purine antagonist that is commonly used for patients with non-Hodgkin lymphoma and chronic lymphocytic leukemia. The most common adverse effects are myelosuppression and immunosuppression. Cardiovascular complications of fludarabine are rare, although several cases of congestive heart failure or left ventricular failure have been reported.\textsuperscript{4,5} There are many possible etiologies for the bradycardia seen in the present patient. For example, sepsis, cardiogenic events, electrolyte imbalance, and drugs such as cytosine arabinoside may all cause bradycardia. An adverse drug reaction is considered to be the probable cause of the bradycardia in this patient because no other etiologies were apparent. Cytosine arabinoside seemed an unlikely cause of bradycardia because the patient had received cytosine arabinoside-containing chemotherapy previously. The bradycardia occurred during fludarabine treatment and subsided significantly after completion of the infusion of this drug. Other probable causes of bradycardia had already been excluded and therefore it is reasonable to speculate about a possible relationship between fludarabine and the sinus bradycardia observed in this patient. Clinicians should be aware of this potential toxic effect of fludarabine, especially in view of its increased use in the treatment of hematologic diseases.

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This article is reprint a that was originally published in the Annals of Saudi Medicine 2010;30(3):246-247.

Bronchiolitis obliterans following hematopoietic stem cell transplantation

To the Editor: One of the most important causes of morbidity and mortality after hematopoietic stem cell transplantation (HSCT) is bronchiolitis obliterans (BO), which sometimes leads to irreversible and progressive air flow obstruction (AFO).\textsuperscript{1,3} Usually this complication is seen after allogeneic transplantation in up to 26% of cases.\textsuperscript{4} The usual diagnostic method is spirometry. Other modalities are high resolution computed tomography (HRCT) and lung biopsy. The most well known and consistent risk factor for BO is chronic graft-versus-host disease (GVHD).\textsuperscript{4,5}

This cross-sectional study was carried out at the Shariati Hospital, Hematology, Oncology and Stem Cell Transplantation Research Center to compare diagnostic methods and to determine additional risk factors by two diagnostic methods. The patients who had allogeneic HSCTs at least six months previously were included in the study and followed from January to June 2009. Exclusion criteria were current smoking or a history of smoking, history of asthma, chronic obstructive pulmonary disease or bronchiectasis, transplantation more than one time and abnormal spirometry with an FEV\textsubscript{1}/FVC less than 70%. All of the patients underwent spirometry and chest HRCT in the inspiratory and expiratory phase. Spirometric criteria for diagnosis of bronchiolitis obliterans without consideration of the age of the patient is defined as FEV\textsubscript{1}/FVC less than 75% or a more than 10% decrement of FEV\textsubscript{1}/FVC from the baseline value. HRCT criteria were air trapping or a mosaic pattern, which is exaggerated on expiratory views. A diagnosis of bronchiolitis obliterans requires one of the spirometric or imaging criteria.

Forty-two patients completed the study. Nineteen (45.2%) met the diagnostic criteria for BO, but only 11 (26.2%) had abnormal spirometry and 17 (40.5%) patients had air trapping and a mosaic pattern in the chest HRCT that was compatible with a diagnosis of BO. Eleven (26.2%) patients had a history of acute GVHD and 21 (50%) had a history of chronic GVHD. Only 10 (23.8%) had no history of acute or chronic GVHD. There was a statistically meaningful correlation between BO and GVHD (P=.037); only one case of BO was in the non-GVHD group (10%), 6 cases in the acute GVHD group (54.5%) and 12 cases were in the chronic GVHD group (57.1%). Ten patients (23.8%) were less than 20 years old, 22 were in the 21-40 year-old group (52.4%) and 10 patients (23.8%) were older than 41 years.