Monitoring of cardiac function on the basis of serum troponin I levels in patients with acute leukemia treated with anthracyclines

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Anthracyclines are used extensively in the therapy of hematologic malignancies. However, their use has been limited by acute and chronic cardiotoxicity. Cardiac troponins have emerged as sensitive and specific markers of even minor myocardial damage. In this study we prospectively evaluated serial measurements of serum cardiac markers and echocardiography in patients with de novo acute myeloid and lymphoid leukemias (AML and ALL, respectively) treated with anthracyclines. We examined and subdivided 79 patients into 3 groups: group 1 (37 patients with AML, all <60 years), group 2 (25 with AML, all ≥60 years), group 3 (17 with ALL). Serum specimens were collected before treatment and during and after therapy and were analyzed for troponin I (TnI), myoglobin, creatine phosphokinase–muscle myocardium isoenzyme B, and lactate dehydrogenase concentrations. In group 1, 4 of the 37 patients (11%) had increased levels of TnI on the 14th day of induction therapy, but by the 28th day the TnI level had returned to normal in 3 of these 4 patients. In group 2, 3 of the 25 patients (12%) demonstrated increased TnI concentrations on the 7th day of induction therapy, but by the 14th day these levels had normalized in 2 of the 3. In group 3, we detected no increased TnI concentrations. Echographic study did show a significant correlation with the TnI levels ($P<.001$), involving a reversible decrease in left ventricular ejection fraction among patients with increased TnI levels (>0.15 ng/mL) on day 14 in group 1 and on day 7 in group 2. These results may aid the clinician in the treatment of patients by identifying high-risk patients who may benefit from closer observation or supportive cardiac therapy. (J Lab Clin Med 2005;145:212–20)

Abbreviations: AIDA = all-trans retinoic acid and idarubicin; AL = acute leukemia; AML = acute myeloid leukemia; ALL = acute lymphoid leukemia; CPK-MMB = creatine phosphokinase–muscle myocardium isoenzyme B; cTnI = cardiac troponin I; ECG = electrocardiography, electrocardiograph; FAB = French-American-British; LDH = lactate dehydrogenase; LFFS = left ventricular fractional shortening; LVDD = left ventricular diastolic diameter; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic diameter; TnI = troponin I; TnT = troponin T

Anthracyclines are chemotherapeutic antimitotic antibiotics that improve the prognosis of several solid and hematologic malignancies in adults and children.[1,2] However, the use of these drugs is limited by their acute, subacute, and chronic/late cardiotoxicity at cumulative doses, which can decrease

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the overall-free survival benefits. Anthracycline-induced cardiomyopathy is characterized by a variety of clinical signs: acute manifestations (within 48 hours of administration) featuring varying degrees of asymptomatic to symptomatic heart block and arrhythmias, subacute manifestations (a few days or weeks after therapy) reflecting cumulative myocyte damage due to low myocardial cell turnover that could induce a "myopericarditis syndrome," and, finally, chronic/late manifestations (months or even years after therapy) involving dilated cardiomyopathy or a delayed form in which myocyte fibrosis leads to restrictive endomyocardial disease, sometimes resulting in overload of both ventricles or congestive heart failure.[3–6]

Many clinical studies have shown that the cardiotoxic effects of anthracyclines develop more frequently in children, and early myocardial disease has been observed after a cumulative doxorubicin dosage of 150 mg/m^2.[7–9]

The authors of 1 review sought to determine the maximum permissible cumulative tolerated doses of different anthracyclines in adult patients beyond which the risk of heart damage is increased (doxorubicin 550 mg/m^2, daunorubicin 600 mg/m^2, epirubicin 1000 mg/m^2, mitoxantrone 160 mg/m^2, zorubicin 1900 mg/m^2).[3]

Cardiotoxicity induced by anthracyclines has been studied extensively in the settings of breast cancer and hematologic malignancy,[1,10–20] but early detection of heart damage during and after therapy with anthracyclines has not been fully investigated in a homogeneous population with acute leukemia.

Endomyocardial biopsy is considered the most sensitive and specific test with which to detect and confirm anthracycline cardiotoxicity; in fact, ultrastructural cellular abnormalities of the myocytes have been found in some patients.[1,2,21,22] Because of the invasiveness of this test, some investigators have studied the myocardial damage induced by anthracyclines with the use of radioactive monoclonal antibodies against cardiac muscle (indium-111–antimyosin scintigraphy) in vivo; in fact, this binding action with free myosin is possible when the cell is disrupted.[7,23]

Serum concentrations of TnI and TnT have emerged as sensitive and specific biomarkers (associated with myofibrillar damage) of various forms of myocardial injury, and the procedures for their determination are noninvasive and inexpensive.[24,25] It has recently been reported that increased serum concentrations of TnI and TnT in patients during treatment with anthracyclines indicate early myocardial damage and predict delayed subclinical cardiac dysfunction, which may become evident weeks or months after chemotherapy.[8,12,16,17,19,20,26–29] In this study we sought to determine the usefulness of sequential monitoring of the cardiac function of adult patients with de novo AL undergoing anthracycline or anthracenedione therapy (eg, daunorubicin, idarubicin, mitoxantrone) in a single institution by conducting prolonged serial measurement of serum cardiac enzymes and assessing echocardiographic and electrocardiographic parameters of heart function.

METHODS

Patients and study protocol. The diagnosis of AML or ALL was made in all cases with the use of peripheral-blood and bone-marrow smears in accordance with standard structural, cytochemical, and immunologic criteria of the FAB and European Group for the Immunological Characterization of Leukemia classification system.[30,31] We carried out leukemic immunophenotypic cell analysis with the use of standard direct or indirect immunofluorescence methods and monoclonal antibodies (Becton Dickinson, San Jose, Calif).

We examined 79 consecutive patients with newly diagnosed AL who were being treated in accordance with the Gruppo Italiano Malattie EMatologiche dell'Adulto–European Organisation for Research and Treatment of Cancer (GIMEMA-EORTC) protocols (AML 10, AML 12, AML 13, AIDA 2000, ALL 2000) at our institution between June 2000 and February 2002 and monitored them until July 2003.

As a means of determining whether different age-related biologic features and comorbidity might influence TnI values during monitoring, we intended to divide patients into groups on the basis of pathologic state (eg, AML and ALL) and into subgroups on the basis of age, but during enrollment only 5 patients older than 60 years were found to have ALL, and they could not be included in the study because their LVEF values were less than 45% (the value under which we did not treat patients with anthracyclines or anthracenediones but with vincristine, prednisone, methotrexate, and 6-mercaptopurine). We therefore established 3 groups: Group 1 comprised 37 patients older than 60 years with AML, group 2 comprised 25 patients 60 years or older with AML, and group 3 comprised 17 patients, all younger than 60 years, with ALL (Table I).

The median age of the patients in group 1 was 48 years (range 14–59 years), and distribution on the basis of FAB criteria was as follows: M0, 2 cases; M1, 4 cases; M2, 15 cases; M3, 3 cases; M4, 6 cases; M4eo, 1 case; M5a, 2 cases; M5b, 2 cases; and M6, 2 cases. The median age of the patients in group 2 was 67 years (range 61–79 years), and distribution on the basis of FAB criteria was as follows: M0, 2 cases; M1, 6 cases; M2, 9 cases; M3, 1 case; M4, 3 cases; M5, 1 case; and M6, 3 cases. The median age of the patients in group 3 (13 with the B phenotype, 4 with the T phenotype) was 42 years (range 15–60 years).

None of the patients had a history of cardiac disease, and we detected no evidence of pretreatment cardiac dysfunction in any patient. The patients received the following chemotherapy (induction and consolidation treatment) protocols involving the use of anthracyclines: Six patients in group 1 were treated with the AML 10 protocol and 28 with the AML 12 protocol, 24 patients in group 2 were treated with the AML 13 protocol and 4 patients classed as M3 were treated with the