SEVERE ADRIAMYCIN CARDIOTOXICITY AT CUMULATIVE DOSE BELOW 500 MG/M2: CASE REPORT AND REVIEW OF THE LITERATURE

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ADRIAMYCIN (doxorubicin hydrochloride), an anthracycline antibiotic originally isolated from the fungus Streptomyces peucetius, is an effective antineoplastic agent against many human neoplasms including leukemias, lymphomas, and many solid tumors such as soft-tissue sarcomas.1 The most serious and total dose-limiting toxicity of Adriamycin is a well-described cardiomyopathy which is thought to be secondary to myocardial damage produced by oxygen-free radical production generated by the drug.1,2 The incidence of Adriamycin-induced cardiac toxicity (AICT) is directly related to the cumulative dose of the drug and is rare at cumulative doses below 550 mg/m2 of body surface area.3

In this report we describe a patient who developed severe Adriamycin-induced cardiomyopathy at a cumulative dose of less than 500 mg/m2. The possible role of other chemotherapeutic agents which the patient was also receiving is also discussed.

Case Report

A 22-year-old Lebanese woman who was suffering from recurrent bouts of profuse vaginal bleeding, which was attributed to a huge uterine fibroid, underwent an abdominal hysterectomy in March 1988, following the failure of repeated dilatation and curettage procedure to control the bleeding. A postoperative pathological diagnosis of high-grade stromal cell sarcoma of the uterus was made. Although there was no evidence of any residual tumor in the postoperative evaluation, the patient experienced tumor recurrence four months later. Adriamycin therapy was then initiated at a dose of 50 mg/m2 to be given at 3 weekly intervals. The patient was still showing evidence of tumor progression despite the completion of six courses of Adriamycin therapy. At this stage, cyclophosphamide (400 mg/m2) and vincristine (2 mg/dose) were introduced while the Adriamycin dose was reduced to 35 mg/m2/3 weeks. The patient was considered to be in partial remission upon completion of five courses of the new regimen that resulted in a total cumulative dose of Adriamycin of 475 mg/m2. A routine MUGA scan demonstrated normal left ventricular function with an ejection fraction of 52%.

One month later, the patient presented with dyspnea on mild exertion and nocturnal cough of few days duration. Clinical signs of congestive heart failure were evident. The electrocardiogram showed sinus tachycardia, generalized low QRS voltage, and poor R wave progression in the chest leads. The chest radiograph showed cardiomegaly, pulmonary congestion, and right-sided pleural effusion (Figure 1). Arterial blood gases obtained on room air revealed severe arterial hypoxemia (P02 = 45 mm Hg). A provisional diagnosis of Adriamycin-induced cardiomyopathy was made and the patient was transferred to the medical intensive care unit. She was started on high concentration of oxygen in addition to aggressive anti-failure therapy. An echocardiogram demonstrated a global cardiac dysfunction consistent with dilated cardiomyopathy. Right thoracentesis was carried out and the findings in the pleural fluid were consistent with transudative effusion with no evidence of malignancy. A Swan-Ganz catheter was placed.

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via the right subclavian approach. Her cardiac index was 3.2 L/m/m²; right atrial pressure, 6 mm Hg; pulmonary capillary wedge pressure, 22 mm Hg; stroke volume index, 21.4 mL/m²; and left ventricular stroke work index, 16.8 g/m/m². Her oxygen delivery index was markedly reduced, 415.6 mL/m/m². The cardiac enzymes remained repeatedly within the normal range. MUGA scan showed marked impairment in ventricular contractility with left ventricular ejection fraction of 23%.

Figure 1. Portable chest radiograph showing cardiomegaly, pulmonary congestion, and right-sided pleural effusion.

The patient showed slow but remarkable improvement in response to treatment with high concentration of oxygen, furosemide, dobutamine, sodium nitroprusside, and captopril. She was discharged from the medical intensive care unit two weeks later in satisfactory condition. She was subsequently discharged from the hospital on oral captopril and furosemide. Despite subjective improvement, a pre-discharge MUGA scan demonstrated the persistence of poor ventricular contractility with an ejection fraction of 18%.

Discussion

AICT is a potentially fatal complication of Adriamycin therapy. Several clinical presentations have been described. These include a wide variety of reversible electrocardiographic changes, acute atrial and ventricular dysrhythmias, a pericarditis-myocarditis syndrome, and a chronic cardiomyopathy. 4 The latter, which usually occurs one to six months after cessation of therapy, is considered to be the severest form of AICT and carries a relatively high mortality rate, approaching 60%, in one of the largest series. 5-7

Although the acute dose-limiting toxicity of Adriamycin is myelosuppression, its unique cardiotoxicity acts as the major determinant of the total dose of the drug to be given. 5 Most authorities recommend discontinuing the drug at a cumulative dose not exceeding 550 mg/m² since the estimated incidence of AICT for such a dose limit is considered low and falls in the range of 0.1% to 0.27%. 3 Nevertheless, some anecdotal reports have described the occurrence of AICT at doses below this dose limit. 8 In addition, few pediatric fatalities have also been reported at lower doses. 9 Other risk factors to develop AICT could, however, have existed in some of these patients. The incidence of AICT rises sharply when the safe dose limit is exceeded, reaching 30% in patients receiving more than 600 mg/m² of Adriamycin. 3,10

In addition to the cumulative dose, other risk factors for AICT have been described. These include advanced age, pre-existing heart disease, uncontrolled hypertension, prior or concomitant mediastinal irradiation, and dosing schedule. 4,11,12 Children have also been described to show a higher rate of this complication than adults. 3

Our patient had had no definite risk factors known to enhance AICT. She had received a cumulative dose of 475 mg/m² which is considered to be within the safe cumulative-dose limits. The estimated risk for such a patient to develop this complication is less than 0.27%, 3 unless a role had been played by the other chemotherapeutic agents given concurrently with Adriamycin, namely, cyclophosphamide and vincristine. In fact, synergistic cardiotoxicity to that of Adriamycin on the heart has been reported with many anti neoplastic agents including cyclophosphamide, mitomycin C, actinomycin D, mithramycin, vincristine, bleomycin, and etoposide. 9,13-16 Nevertheless, the true synergism of many of these agents has never been documented since most of the available data originate from single case reports and small series which makes their true contribution to AICT speculative. The only possible exception to the latter statement is cyclophosphamide since acute cardiac toxicity following
large doses of cyclophosphamide is a well-known phenomenon and is thought to be enhanced by prior use of anthracyclines.17,18 Definite evidence for the role of low doses of cyclophosphamide in potentiating AICT is, however, lacking.3,10 Thus, the true role of the concomitant use of cyclophosphamide in our patient in enhancing AICT remains questionable.

In addition to total-dose limitations, various attempts have been made to prevent AICT. These include serial cardiac function monitoring by invasive and noninvasive techniques and manipulation of the dosing schedule.19 Nevertheless, repeated careful clinical examination and dose limitations are still the simplest, least expensive, and reliable guides for the proper use of anthracyclines in patients with no definite risk factors to develop AICT.20,21 Routine cardiac function monitoring in patients without risk factors is not generally recommended nor considered cost-effective.2,21 However, monitoring of the cardiac function with noninvasive technique, such as radionuclide ejection fraction determination, and by invasive technique, such as repeated endomyocardial biopsies, may become necessary when Adriamycin is to be used in patients with pre-existing risk factors in whom the use of the drug is felt to be superior to all other available alternatives and in patients in whom the upper limit of the presumed safe-dose limit has been reached while still harboring Adriamycin-sensitive tumor; discontinuation of the drug for these patients is not an affordable option.

The prevention of AICT has also been attempted through the use of various pharmacological agents, including free-radical scavengers such as alphatocopherol (vitamin E) and acetylcysteine, betablockers, carnitine, calcium-channel blockers, and digoxin. Unfortunately, none of these agents has shown proven reproducible efficacy in protecting against AICT.12,22 The only promising agent is the recently described EDT A (ethylenediamine tetraacetic acid) analogue known as ICRF-187 (Bispiperzinedione ICRF-87) which is still the subject of an extensive ongoing research although the preliminary results are quite encouraging.2,23

References
