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Fatal esorubicin-induced cardiomyopathy: report of a case and review of the literature*, **

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Summary. A case of fatal dilated cardiomyopathy induced by esorubicin (ESO) at a total dose of 740 mg/m^2, given in 27 doses over 650 days, is reported. The sudden onset, rapid clinical deterioration, and fatal outcome are detailed. The outcome was not predicted by serial rest ejection fractions or clinical signs. The data from animal studies, phase 1 and phase 2 clinical testing, are reviewed, demonstrating the almost complete absence of reports of ESO-induced cardiotoxicity. Studies reviewing ejection fractions and myocardial biopsy scores show that ESO can be cardiotoxic and may produce fatal dilated cardiomyopathy.

Introduction

Doxorubicin has the widest spectrum of activity of any therapeutic antineoplastic agent. Its dose-limiting chronic toxicity, cardiomyopathy, has been a major problem. Esorubicin (ESO), synthesized by removing the hydroxyl group from the 4' position on the amino sugar moiety of doxorubicin, was developed to enhance the therapeutic index and decrease the cardiotoxicity of doxorubicin [29]. Initial testing in animals has demonstrated that it was potentially more active and less cardiotoxic than doxorubicin [9–12, 22]. Phase 1 testing has demonstrated no cardiotoxicity [14, 16, 26–28], and phase 2 studies have shown that there was minimal cardiac toxicity [1, 4–6, 8, 13, 15, 17, 18, 20, 21, 23, 24, 30]. However, studies of ejection fractions by quantitative radionuclide angiocardiography (LVEF) have demonstrated decreases in ejection fractions of some patients treated with ESO [25]. Studies of myocardial biopsies have also demonstrated myocardial damage secondary to this drug [7]. There is only one reported case of a nonfatal cardiomyopathy in a patient without prior heart disease [3]. In this report, we detail the clinical, functional, and pathological changes in a patient who died from ESO-induced dilated cardiomyopathy, and the literature is reviewed.

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Case report

A 58-year-old woman had a right radical mastectomy in 1968 and a left modified radical mastectomy in 1975, both for infiltrating ductal carcinoma. In January 1985, a chest X-ray demonstrated two nodules in the left lung and one in the right lung. Tomograms of the lung demonstrated multiple bilateral pulmonary nodules. Transbronchial lung biopsies demonstrated undifferentiated carcinoma, consistent with breast cancer. In February 1985, she developed a symptomatic right parietal-occipital mass lesion. Whole brain irradiation was given. She was then started on a Cancer and Leukemia Group B (CALGB) phase 2 protocol to receive ESO at 30 mg/m^2. Her cardiac history, examination, and EKG were normal. A rest LVEF was 68% with normal segmental and global wall motion. The lung nodules gradually decreased in size until a normal chest X-ray was obtained in October 1985. She continued treatment according to protocol, to receive ESO every 3 weeks and rest LVEF every 3 months. On November 18, 1986, because of severe anemia and fatigue, she received 3 units of packed red blood cells over 24 h with i.v. furosemide between the units. Over the next 24 h she developed increased shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea. On physical examination, she had rales, a third heart sound, and a diffuse apical impulse in the anterior axillary line. A chest X-ray showed a new left pleural effusion. Thoracentesis demonstrated a transudate. Over the next 3 weeks she developed altered mental status and congestive hepatomegaly. Her ejection fraction was 19% with global hypokinesia. She developed cardiogenic shock and died on December 24, 1986, of refractory ventricular dysrhythmias. Details of the dose, schedule, ejection fractions, and clinical events are shown in Fig. 1.

An autopsy demonstrated cardiomegaly with four-chamber dilatation and mild hypertrophy (heart weight, 375 g). The coronary arteries were widely patent. Valvular architecture was unremarkable. Histologic sections of the myocardium revealed widespread interstitial edema, with scattered myocytes showing vacuolar degeneration of the cytoplasm. There were no inflammatory infiltrates. Electron microscopy showed loss of myofibrils, although this effect may have been due to postmortem autolytic changes. These findings were interpreted as indicating dilated cardiomyopathy without evidence of underlying chronic cardiovascular disease. A fortuitous finding was two microscopic foci of metastatic carcinoma in the lungs, which were not evident by gross examination.

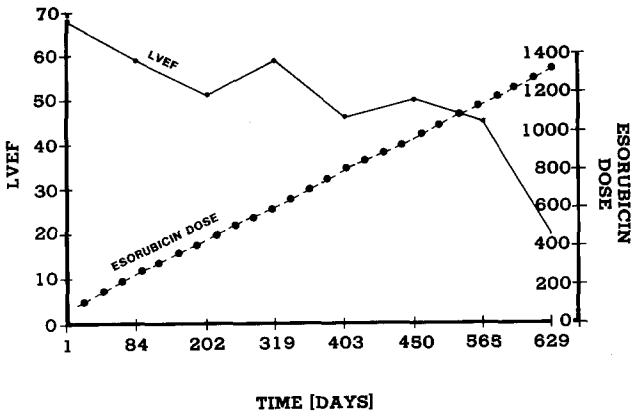

Fig. 1. Patient data: Esorubicin dose and left ventricular ejection fraction as a function of time on treatment

Discussion

This patient developed clinical, fatal, dilated cardiomyopathy after receiving a total dose of 1386 mg ESO (740 mg/m^2) in 27 doses over 22 months. Because the CALGB protocol permitted patients with no prior treatment to be placed under study, she had no prior chemotherapy or irradiation; she also had no prior evidence of heart disease or risk factors for heart disease. Her unequivocal, complete response, absence of signs or symptoms of heart failure, stable and adequate ejection fraction, and our concern regarding recurrence if the drug were stopped, as well as the virtual absence of reported cases of ESO cardiotoxicity all contributed to the long course and high total drug dose. The heart failure was rapid in onset, not predicted by symptoms, physical examination, or serial rest ejection fractions and was rapidly fatal, with 36 days between onset and death. Autopsy findings in anthracycline-induced cardiomyopathy have included biventricular dilatation with mild hypertrophy. By light microscopy, disseminated foci of interstitial edema and fibrosis with vacuolar degeneration of cardiac cells can be seen. Electron microscopic examination has revealed myofibrillar dropout and swelling of the sarcoplasmic reticulum [2, 19]. Our case reflects these findings to a large degree. Although interstitial fibrosis was less prominent than edema, this change may reflect the lack of chronicity seen in the patient's course. EM changes were difficult to interpret due to the presence of autolytic changes. The pathologic findings clearly excluded etiologies of heart disease in which diagnostic tissue changes are present.

Results of cardiac toxicity studies in animals were in striking contrast to the findings with doxorubicin. ESO has produced minimal morphological changes in the heart of the mouse, and none in the rabbit [9–12, 22]. Further studies in the rat have demonstrated significantly less cardiotoxicity for ESO than for doxorubicin, and studies in mice have demonstrated greater potency for ESO than for doxorubicin [9]. Thus, the therapeutic ratio between cardiotoxic doses and antitumor doses were predicted to be almost three times better for ESO than for doxorubicin [9].

Two hundred twenty patients have been evaluated in five phase 1 studies (Table 1). Only one patient had dilated cardiomyopathy, and that was attributable to underlying heart disease. Of the 30 patients studied by LVEF, only four had abnormal LVEF. Two LVEFs were abnormal posttreatment in patients without prior scans, and in two patients LVEF decreased from previously normal values.

Table 1. Esorubicin cardiac toxicity

Reference	Phase	Type of cancer	Total patients	No. with heart failure	Abnormal LVEF	Dose (mg/m^2)
16	I	Mixed	36	0/34	0/3	25–222[a]
28	I	Mixed	60	0/56	2/7	10–250[b]
14	I	Mixed	73	1/65	2/20	< 340[c]
27	I	Mixed	26	0/26		
26	I	Mixed	25	0/25		
18	II	Kidney	15	0/15	0/15	
13	II	Colo/rectal	33	0/31	8/23	75–645[d]
6	II	Prostate	15	0/14		
15	II	Colo/rectal	32	0/32	0/9	
24	II	Lung	87	0/83		
20	II	Breast	20	0/20	0/7	45–120[e]
30	II	Kidney	23	0/23		
21	II	Colo/rectal	25	0/25		
5	II	Breast	25	0/24	3/24	175
23	II	Sarcoma	22	0/22	2/7	135–215[f]
8	II	Breast	27	0/23		
4	II	Gastric/pancreatic	29	0/29	2/–	70–184[f]
17	II	Kidney	16	0/15		
1	II	Colo/rectal	45	0/34		

[a] 1 nondrug-related infarct
[b] LVEF = 30% after 75 mg/m^2 and LVEF = 48% after 160 mg/m^2, which increased to LVEF = 55% while ESO therapy continued
[c] LVEF decreased 67%–47% with heart failure in patient with prior heart disease; LVEF decreased 77%–54% in asymptomatic patient
[d] 8 patients had LVEF decrease > 10% at doses of 75–640 mg
[e] Doses are only for patients having LVEF
[f] Doses for patients with decreased LVEF

It should be stressed that the highest dose of ESO reported in these trials was 340 mg/m^2 (Table 1). Most patients received substantially lower doses.

In phase 2 testing, 414 patients have received ESO [1, 4–6, 8, 13, 15, 17, 18, 20, 21, 23, 24, 30]. Data on toxicity for 390 revealed only one case of congestive heart failure, attributed to the patient's sepsis. Fifteen patients had a decrease in their LVEF of > 10%. As in the phase 1 studies, the doses in the phase 2 studies were relatively low (Table 1), possibly too low to reveal chronic dose-related cardiotoxicity.

Two other pieces of data suggest that ESO is cardiotoxic. In 82 patients treated in a phase 2 study of non-small-cell lung cancer with ESO given at 30 mg/m^2 i.v. every 21 days, there was a trend toward a decrease in ejection fraction of 5%–10% beginning at a cumulative drug dose of 220 mg/m^2 [25]. Five patients developed signs or symptoms of congestive heart failure: one was secondary to pericardial effusion, one was related to new onset angina, and three were otherwise unexplained.

A review by investigators from the Northern California Oncology Group of eleven endomyocardial biopsies in patients receiving ESO demonstrated Billingham scores of 1.0–2.5 [7]. Additionally, two of four patients had a decreased ejection fraction. These investigators concluded that ESO has significant cardiotoxicity.

A single case report of ESO-induced cardiomyopathy has been published [3]. This patient was a 54-year-old woman treated with a total dose of 184 mg/m^2 who developed a decreased ejection fraction (64% decreasing to 51%) with diffusely abnormal wall motion. She did not have symptoms of congestive heart failure.

There are a number of similarities between our patient and patients reported to have doxorubicin cardiotoxicity. In doxorubicin cardiotoxicity, damage steadily accumulates, symptoms can be acute at onset, cardiomyopathy occurs shortly after the last dose, and progression is frequent and rapid [19]. In the patient reported here, the LVEF initially decreased but then stabilized at > 45%. The patient had no symptoms of cardiac disease until the sudden clinical deterioration. The onset of symptomatic dilated cardiomyopathy was acute, occurred soon after the last dose of ESO, and was rapidly fatal. Of major importance was the lack of sensitivity of serial rest LVEF in predicting progressive cardiac disease and the sudden onset of heart failure.

We conclude that ESO can be a significantly cardiotoxic agent. This report details the first case of fatal cardiotoxicity induced by ESO.

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