Congestive Heart Failure in Patients Treated with Doxorubicin

A Retrospective Analysis of Three Trials

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BACKGROUND. Doxorubicin is a highly effective and widely used cytotoxic agent with application that is limited by cardiotoxicity related to the cumulative dose of the drug. A large-scale study that retrospectively evaluated the cardiotoxicity of doxorubicin reported that an estimated 7% of patients developed doxorubicin-related congestive heart failure (CHF) after a cumulative dose of 550 mg/m^2. To assess whether this estimate is reflective of the incidence in the broader clinical oncology setting, the authors evaluated data from three prospective studies to determine both the incidence of doxorubicin-related CHF and the accumulated dose of doxorubicin at which CHF occurs.

METHODS. A group of 630 patients who were randomized to a doxorubicin-plus-placebo arm of three Phase III studies, two studies in patients with breast carcinoma and one study in patients with small cell lung carcinoma, were included in the analysis.

RESULTS. Thirty-two of 630 patients had a diagnosis of CHF. Analysis indicated that an estimated cumulative 26% of patients would experience doxorubicin-related CHF at a cumulative dose of 550 mg/m^2. Age appeared to be an important risk factor for doxorubicin-related CHF after a cumulative dose of 400 mg/m^2, with older patients (age $>$ 65 years) showing a greater incidence of CHF compared with younger patients (age $\leq$ 65 years). In addition, $>$ 50% of the patients who experienced doxorubicin-related CHF had a reduction $<$ 30% in left ventricular ejection fraction (LVEF) while they were on study.

CONCLUSIONS. Doxorubicin-related CHF occurs with greater frequency and at a lower cumulative dose than previously reported. These findings further indicate that LVEF is not an accurate predictor of CHF in patients who receive doxorubicin.
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Doxorubicin is one of the most widely prescribed and effective cytotoxic drugs used in oncology. However, the utility of doxorubicin is limited by cumulative, dose-related, progressive myocardial damage that may lead to congestive heart failure (CHF). Thus, patients who may benefit from continued administration of the drug must withdraw from doxorubicin therapy and switch to an alternative agent, which may be less effective.

In a retrospective analysis, Von Hoff et al.[1] identified total cumulative dose as a major risk factor for doxorubicin-related CHF. Those authors reported that there was a continuum of increasing risk with

increasing total dose: The estimated cumulative percentage of patients who developed CHF at a cumulative doxorubicin dose of 400 mg/m^2 was 3%, increasing to 7% at 550 mg/m^2 and to 18% at 700 mg/m^2. It also was shown that doxorubicin-related CHF was schedule dependent: The incidence was lower with a once-weekly schedule, compared with a once 3-weekly schedule, of doxorubicin administration. In addition, it was found that increasing age was associated with an increasing risk of doxorubicin-related CHF.

We previously reported the results of two Phase III trials of similar design that were initiated in February 1988 (Study 088001) and May 1989 (Study 088006) that prospectively assessed the cardioprotective efficacy of dexrazoxane (DZR) in patients who were receiving fluorouracil, doxorubicin, and cyclophosphamide (FAC) combination therapy for advanced breast carcinoma.[2,3] The results of those studies indicated that DZR provided significant cardioprotection,[2] even if treatment started after a cumulative doxorubicin dose of 300 mg/m^2 had been administered.[3]

The 2.2% incidence of doxorubicin-related CHF reported by Von Hoff et al.[1] may not have been an accurate reflection of the true incidence of this adverse event. Those authors speculated that the incidence may have been underestimated due to low doses of doxorubicin administered to many of the patients, limitation of CHF reporting to investigator-observed CHF symptoms secondary to doxorubicin, and the "usual limitations" of a retrospective study.[1] To determine whether the incidence of doxorubicin-induced CHF is higher than that suggested by Von Hoff et al., we analyzed data from patients in the placebo arms of the 088001 and 088006 breast cancer trials[2,3] together with data from patients in the placebo arm of the 088002 lung carcinoma trial, which was a Phase III study of cyclophosphamide, doxorubicin, and vincristine (CAV), administered with or without DZR, in patients with advanced small cell lung carcinoma.[4] The primary objective of this analysis was to examine the relationship between the cumulative doxorubicin dose and the cumulative probability of developing doxorubicin-related CHF. The effect of doxorubicin dose on cardiac events, including predefined falls in ejection fraction, also was evaluated in this manner.

MATERIALS AND METHODS

Patient Characteristics

Patients who were included in the current analysis were enrolled in three randomized, double-blind, multicenter studies that evaluated cardiotoxicity in patients receiving DZR and a doxorubicin-containing regimen for breast carcinoma or small cell lung carcinoma. In the first two studies (088001 and 088006), patients with advanced breast carcinoma received 5-fluorouracil, 500 mg/m^2; doxorubicin, 50 mg/m^2; and cyclophosphamide, 500 mg/m^2 intravenously (i.v.) every 3 weeks and were randomized to receive either DZR (500 mg/m^2 or 1000 mg/m^2) or placebo.[2,3] There was no maximum dose for doxorubicin, and no patients had received anthracyclines previously. The protocols for Studies 088001 and 088006 were identical. In the third study (088002), chemotherapy-naïve patients with advanced small cell lung carcinoma received cyclophosphamide, 500 mg/m^2; doxorubicin, 50 mg/m^2; and vincristine, 2.0 mg, all i.v., every 3 weeks and were randomized to receive either DZR (500 mg/m^2 or 1000 mg/m^2) or placebo.[4] The protocol for Study 088002 was similar to the protocols for the other two studies.

During the studies, there was clear evidence of significant cardioprotection with DZR; and, for this reason, the study protocols were amended to ensure maximum patient benefit from DZR. In all three studies, patients who were randomized to receive placebo after January 14, 1991 received open-label DZR starting with their seventh cycle of treatment. Patients who were randomized to receive placebo before January 14, 1991 and who had completed at least six cycles of treatment by that date received open-label DZR starting with their next cycle.

All patients who were randomized to the placebo arms of these studies were included in the current intent-to-treat analysis. Patients were enrolled between February 1988 and December 1992 in Study 088001; between February 1988 and January 1991 in Study 088002; and between May 1989 and December 1992 in Study 088006. Data were collected from a total of 630 placebo-treated patients: 348 patients in Study 088001, 111 patients in Study 088002, and 171 patients in Study 088006. Among these patients, 168 patients (27%) subsequently switched to open-label DZR after January 14, 1991: 91 patients (26%) in Study 088001, 13 patients (12%) in Study 088002, and 64 patients (37%) in Study 088006. The data for these patients were censored, as discussed below.

Evaluation

All patients had a left ventricular ejection fraction (LVEF) equal to or greater than the defined lower limit of normal (LLN) for the institution when they were assessed within 4 weeks of entry into the trial. Exclusion criteria were a documented history of heart failure or current heart failure, mycardiopathy or current arrhythmia (atrial fibrillation or flutter or ventricular arrhythmia, except for occasional unifocal premature

ventricular contractions), or an episode of myocardial infarction within the past 6 months.

Multiple-gated acquisition (MUGA) nuclear scans for assessment of resting LVEF were performed at each institution at baseline and after cumulative doxorubicin doses of 150 mg/m^2, 300 mg/m^2, 400 mg/m^2, and 500 mg/m^2 and at every 50 mg/m^2 dose increment thereafter. Scans were repeated if they were abnormal, and the results of the second scan were used for decision-making. The protocol definition of CHF included two or more of the following: cardiomegaly on chest X-ray; basilar rales; S_3 gallop; or either paroxysmal nocturnal dyspnea, orthopnea, or significant dyspnea on exertion. Standardized assessments by an oncologist were performed for each patient at the cumulative doses stated above. Patients with signs or symptoms possibly related to CHF were identified and assessed to determine the likelihood that these either were a manifestation of true CHF or were related to the underlying malignancy or its progression. Shortness of breath attributed to lymphangetic tumor spread and malignant pericardial effusion were considered sequelae of tumor progression rather than evidence of primary cardiac disease. When signs and symptoms were attributed to a cardiac etiology, their likely relation to doxorubicin was rated on a scale from 0 to 5, with 0 indicating no possibility of doxorubicin involvement and 5 indicating a strong probability of doxorubicin cardiotoxicity. This assessment was based on total cumulative doxorubicin dose; initial cardiac systolic function (based on MUGA); changes in cardiac systolic function over time (based on MUGA); electrocardiographic changes; and additional information, such as results of chest X-ray, other imaging studies, or laboratory values. The possibility of multiple etiologies contributing to the clinical picture was taken into account. This semiquantitative assessment scale served as the basis for determining the incidence of cardiotoxicity: Patients with higher scores (3–5) were considered to have doxorubicin-related CHF. These determinations were made by a cardiologist (M.S.E.) without knowledge of the treatment arm to which patients had been assigned. In addition, CHF symptoms, cumulative doxorubicin dose, and the overall clinical picture were reviewed by the cardiologist to ensure that patients were classified appropriately with doxorubicin-related CHF. The cumulative dose at which doxorubicin-related CHF occurred was considered the cumulative dose that had been administered at the latest treatment cycle. Patients were followed to determine whether they had experienced CHF at any time, either on study or off study.

Cardiac Events

A cardiac event was defined as a decline in absolute value $\geq$ 20% in LVEF from baseline, a decline in absolute value $\geq$ 10% in LVEF from baseline and to below the institution's LLN, a postbaseline decline in absolute value $\geq$ 5% in LVEF below the institution's LLN, or the occurrence of CHF on study. For most institutions, the LLN for LVEF was 50%.

Statistical Methods

The cumulative proportion of patients who experienced doxorubicin-related CHF at a given cumulative doxorubicin dose was estimated with a Kaplan–Meier curve using cumulative doxorubicin dose as the "time" axis. This included CHF that occurred on study and off study. Patients who received open-label dexrazoxane were censored at the highest cumulative dose that could have been associated with CHF prior to initiation of open-label dexrazoxane. This was the cumulative dose at their last MUGA scan prior to dexrazoxane initiation. Otherwise, patients who did not have CHF either on or off study were censored at the cumulative dose after their last treatment cycle.

Kaplan–Meier curves also were estimated for selected patient subgroups. The categories of subgroups included age ($\leq$ 65 years or $>$ 65 years), history of cardiovascular disease (yes or no), LVEF within 10% of the institution's LLN (yes or no), Eastern Cooperative Oncology Group performance status (0, 1, or $>$ 1), race (white, black, or other), and gender (for Study 088002 only). Intragroup comparisons were performed using the generalized Wilcoxon test and *P* values computed for descriptive purposes. Hazard ratios for patients in each subgroup who had at least one CHF risk factor within a given category were estimated using a Cox proportional hazards model. Cox proportional hazards models with studies included in the model as covariables also were investigated. Exposure to chest irradiation also was tabulated for patients with doxorubicin-related CHF.

The cumulative proportion of patients who experienced an on study cardiac event at a given cumulative doxorubicin dose also was estimated using a Kaplan–Meier curve, and these patients were censored, as described above. SAS software (version 6.12; SAS Institute Inc., Cary, NC) was used for all analyses.

RESULTS

Patient Baseline Characteristics

Patient demographics and baseline clinical characteristics are summarized in Table 1 for individual and combined studies. The median age for all patients was 59 years (range, 23–82 years). The median ages were

TABLE 1
Demographics and Baseline Clinical Characteristics of the Study Populations

Patient characteristics	No. of patients (%)			
	Study 088001 (n = 348 patients)	Study 088002 (n = 111 patients)	Study 088006 (n = 171 patients)	All studies (n = 630 patients)
Age				
≤ 65 yrs	273 (78)	57 (51)	128 (75)	458 (73)
> 65 yrs	75 (22)	54 (49)	43 (25)	172 (27)
History of heart disease				
No	322 (93)	88 (79)	147 (86)	557 (88)
Yes	26 (7)	23 (21)	24 (14)	73 (12)
LVEF < 10% above LLN				
No	266 (76)	79 (71)	123 (72)	468 (74)
Yes	82 (24)	32 (29)	48 (28)	162 (26)
ECOG performance status				
0	182 (52)	34 (31)	100 (58)	316 (50)
1	140 (40)	53 (48)	63 (37)	256 (41)
2	26 (7)	24 (22)	7 (4)	57 (9)
3	0 (0)	0 (0)	1 (1)	1 (< 1)
Race				
White	244 (70)	103 (93)	138 (81)	485 (77)
Black	64 (18)	7 (6)	23 (13)	94 (15)
Other	40 (11)	1 (1)	10 (6)	51 (8)
Gender				
Female	348 (100)	38 (34)	171 (100)	557 (88)
Male	0 (0)	73 (66)	0 (0)	73 (12)

LVEF: left ventricular ejection fraction; LLN: lower limit of normal; ECOG: Eastern Cooperative Oncology Group.

56.5 years for patients in Study 088001, 65 years for patients in Study 088002, and 57 years for patients in Study 088006. Patients in the lung carcinoma study (088002) were older and had a poorer performance status compared with patients in the breast carcinoma studies. Nearly 50% of patients in Study 088002 were older than 65 years compared with ≈ 25% of patients in Studies 088001 and 088006. In addition, a greater proportion of patients in Study 088002 were white. Sixty-five percent of patients in Study 088002 were male; however, because the 2 breast carcinoma studies were restricted to females, overall, only 12% of patients in the current analyses were male.

Congestive Heart Failure

The number of patients with doxorubicin-related CHF and the number per patient dose of doxorubicin exposure (based on a 50 mg/m^2 aliquot) are presented for the individual and combined studies, in addition to the above-defined patient subgroups, in Table 2. The 630 patients were exposed to a total of 178,500 mg/m^2 of doxorubicin (3570 doses). Thirty-two of those 630 patients (5.1%) had doxorubicin-related CHF, representing 0.0090 events per patient-dose of exposure.

The numbers of patients at risk, the numbers of doxorubicin-related CHF events, and the estimated cumulative percentage of patients with doxorubicin-related CHF at a given cumulative doxorubicin dose are presented for all three studies, separately and combined, in Tables 3 and 4. The majority of the events occurred at cumulative doses of ≥ 500 mg/m^2. Overall, the estimated cumulative percentage of patients with doxorubicin-related CHF was 5% at a cumulative dose of 400 mg/m^2, rising to 16% at a dose of 500 mg/m^2, 26% at a dose of 550 mg/m^2, and 48% at a dose of 700 mg/m^2 (Fig. 1). The standard error of these estimates increased as the cumulative dose increased, due in part to the smaller numbers of patients at risk.

Ten of 172 older patients (5.8%) experienced doxorubicin-related CHF, compared with 22 of 458 younger patients (4.8%). The estimated cumulative percentages of patients in each age group who experienced doxorubicin-related CHF at a given cumulative doxorubicin dose are shown in Figure 2. The hazard ratio for doxorubicin-related CHF in older patients relative to younger patients was 2.25 (95% confidence interval [95% CI], 1.04–4.86). Because the difference between the 2 groups was apparent only after a cumulative doxorubicin dose of 400 mg/m^2, the P value associated with this comparison is large (P = 0.78; generalized Wilcoxon test). Adjusting for covariables in the proportional hazards model, the hazard ratio

TABLE 2
Number of Patients with Doxorubicin-Related Congestive Heart Failure and Number per Patient-Dose (50 mg/m^2) of Doxorubicin Exposure for Various Subgroups

	No. of patients with CHF (no. per patient-dose of exposure × 1000)			
Patient characteristics	**Study 088001**	**Study 088002**	**Study 088006**	**All studies**
Age				
≤ 65 yrs	16 (10)	2 (6)	4 (5)	22 (8)
> 65 yrs	5 (12)	4 (15)	1 (5)	10 (11)
History of heart disease				
No	19 (10)	6 (12)	5 (6)	30 (9)
Yes	2 (15)	0 (0)	0 (0)	2 (6)
LVEF < 10% above LLN				
No	16 (10)	5 (12)	5 (7)	26 (10)
Yes	5 (11)	1 (6)	0 (0)	6 (7)
ECOG status				
0	14 (13)	3 (15)	5 (9)	22 (12)
1	7 (9)	0 (0)	0 (0)	7 (5)
2–3	0 (0)	3 (25)	0 (0)	3 (11)
Race				
White	18 (12)	6 (11)	4 (5)	28 (10)
Black	3 (9)	0 (0)	1 (9)	4 (9)
Other	0 (0)	0 (0)	0 (0)	0 (0)
Gender				
Female	21 (10)	2 (10)	5 (5)	28 (9)
Male	—	4 (10)	—	4 (10)
Total	21 (10)	6 (10)	5 (5)	32 (9)

CHF: congestive heart failure; LVEF: left ventricular ejection fraction; LLN: lower limit of normal; ECOG: Eastern Cooperative Oncology Group.

TABLE 3
Number of Patients at Risk and Number of Patients with On Study or Off Study, Doxorubicin-Related Congestive Heart Failure, by Cumulative Dose

	No. of patients at risk/no. of events							
	Study 088001 (n = 348 patients, 21 events)		**Study 088002 (n = 111 patients, 6 events)**		**Study 088006 (n = 171 patients, 5 events)**		**All studies (n = 630 patients, 32 events)**	
Dose (mg/m^2)	**At risk**	**Events**	**At risk**	**Events**	**At risk**	**Events**	**At risk**	**Events**
150	310	1	94	0	150	0	554	1
300	226	4	62	2	100	0	388	6
400	81	3	22	1	28	0	131	4
450	54	0	16	2	20	1	90	3
500	44	5	10	0	17	1	71	6
550	23	4	6	0	12	1	41	5
600	10	1	6	0	7	1	23	2
650	7	2	1	0	5	1	13	3
700	3	0	1	0	3	0	7	0
750	2	0	1	0	2	0	5	0
800	2	0	1	0	2	0	5	0
850	1	1	1	1	0	0	2	2

dropped slightly to 2.12 (95% CI, 0.96–4.68). However, after a cumulative doxorubicin dose of 400 mg/m^2, the hazard ratio increased to 3.28 (95% CI, 1.40–7.65; $P = 0.002$; generalized Wilcoxon test).

Other subgroup comparisons did not yield hazard ratios that differed appreciably from unity. In Studies 088001 and 088006, 9 of 26 patients who experienced CHF had received radiation to the left chest wall or mediastinum. One patient in Study 088002 had received radiation to the chest wall or mediastinum;

TABLE 4
Estimated Cumulative Percentage of Patients with On Study or Off Study, Doxorubicin-Related Congestive Heart Failure, by Cumulative Dose

	Cumulative percentage and SE							
	Study 088001 (n = 348 patients, 21 events)		Study 088002 (n = 111 patients, 6 events)		Study 088006 (n = 171 patients, 5 events)		All studies (n = 630 patients, 32 events)	
Dose (mg/m^2)	%	SE	%	SE	%	SE	%	SE
150	0.3	0.3	0.0	—	0.0	—	0.2	0.2
300	2.1	0.9	3.2	2.2	0.0	—	1.7	0.6
400	5.7	2.2	7.6	4.8	0.0	—	4.7	1.6
450	5.7	2.2	19.2	8.7	5.0	4.9	7.9	2.4
500	16.4	4.9	19.2	8.7	10.6	7.1	15.7	3.7
550	31.0	7.8	19.2	8.7	18.0	9.7	26.0	5.4
600	37.9	9.6	19.2	8.7	29.8	13.6	32.4	6.6
650	55.6	12.6	19.2	8.7	43.8	16.6	48.0	9.4
700	55.6	12.6	19.2	8.7	43.8	16.6	48.0	9.4
750	55.6	12.6	19.2	8.7	43.8	16.6	48.0	9.4
800	55.6	12.6	19.2	8.7	43.8	16.6	48.0	9.4
850	100.0	—	100.0	—	—	—	100.0	—

SE: standard error.

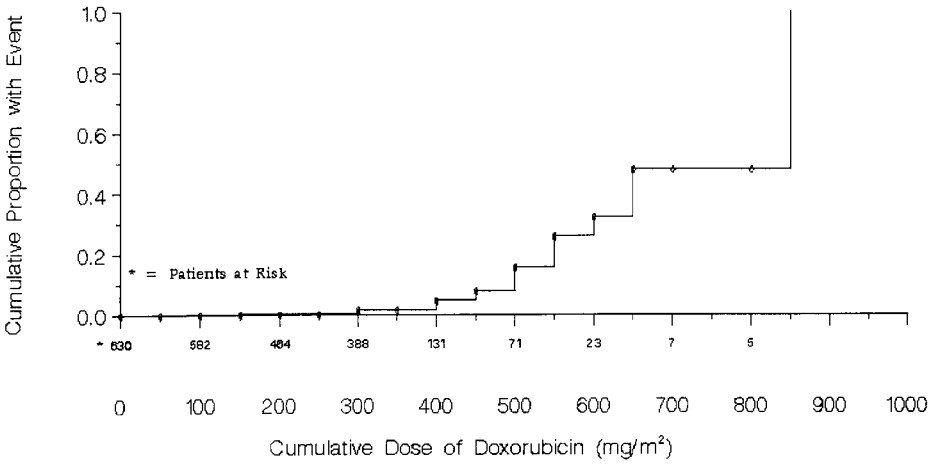

FIGURE 1. Cumulative doxorubicin dose at onset (on study or off study) of doxorubicin-related congestive heart failure in 630 patients who were randomized to receive a doxorubicin-containing regimen plus placebo.

therefore, overall, 10 of 32 patients received this type of radiation. However, radiation exposure could not be ascertained reliably (due to incomplete reporting in case report forms) for patients who did not develop doxorubicin-related CHF; thus, it was not possible to determine whether radiation was a important risk factor for CHF.

Symptom-related characteristics of the 32 patients with doxorubicin-related CHF are summarized as follows: Twelve patients (38%) had mild symptoms (New York Heart Association [NYHA] Class I or II), 11 patients (34%) experienced moderate symptoms (NYHA Class III), and 9 patients (28%) experienced severe symptoms (NYHA Class IV).[5] Twenty-nine patients (91%) experienced an on study cardiac event, and 11 patients (34%) experienced on study CHF. Twenty-one patients (66%) had declines in LVEF of 0–30% (absolute value) from baseline levels while on study: One patient (3%) had a decline $<$ 10%, 11 patients (34%) had declines of 10–20%, and 9 patients (28%) had declines of 20–30%. Eleven patients (34%) had reductions $\geq$ 30% from their baseline LVEF values: Nine patients had decreases 30–40%, and 2 patients had decreases $\geq$ 50%. The two patients with reductions $\geq$ 50% in LVEF had severe CHF symptoms; otherwise, there was no relationship between CHF severity and the decline in LVEF (data not shown). Twenty of these 32 patients died of progressive dis-

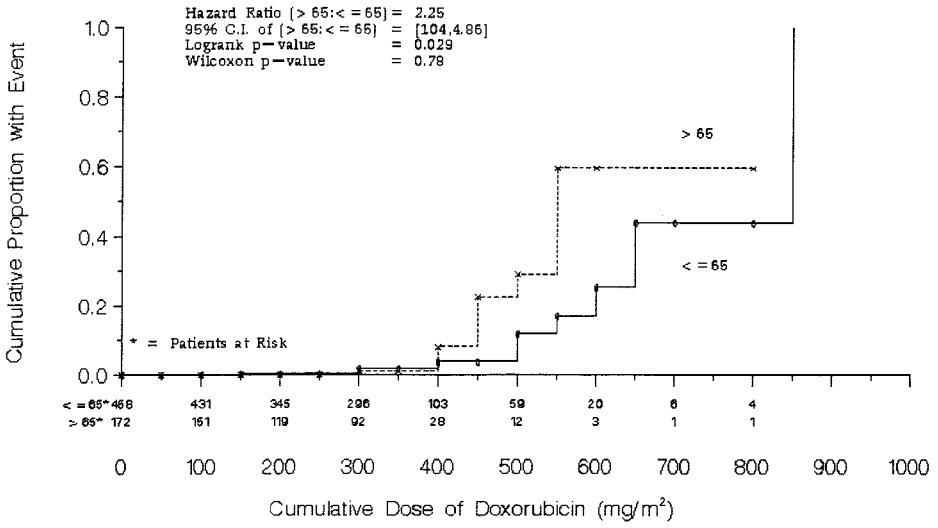

FIGURE 2. Cumulative doxorubicin dose at onset (on study or off study) of doxorubicin-related congestive heart failure in 630 patients who were randomized to receive a doxorubicin-containing regimen plus placebo according to age in patients age 65 years or younger (line with circles) and patients older than 65 years (line with crosses). Circles and crosses indicate censored patients. 95% CI: 95% percent confidence interval.

ease, 5 patients died of progressive disease and CHF, 1 patient died of CHF, 1 patient died of a cerebrovascular accident, 1 patient had a sudden death, 1 patient was lost to follow-up, and 3 patients were alive at the termination of the study follow-up. The patient who died of CHF, who had received a cumulative doxorubicin dose of 450 mg/m^2, had two risk factors for cardiomyopathy: age $>$ 65 years and a history of hypertension.

Cardiac Events

Overall, 149 of 630 patients who received doxorubicin experienced a cardiac event on study. The number of patients at risk, the number of events, and the estimated cumulative percentage of patients with on-study cardiac events are summarized for all three studies, both separate and combined, in Tables 5 and 6. The estimated cumulative percentages also are displayed in Figure 3 for all three studies combined. Overall, the estimated cumulative percentage of patients who experienced an on study cardiac event was 7% at a cumulative doxorubicin dose of 150 mg/m^2, increasing to 9%, 18%, 38%, and 65% of patients at cumulative doses of 250 mg/m^2, 350 mg/m^2, 450 mg/m^2, and 550 mg/m^2, respectively.

DISCUSSION

The incidence of doxorubicin-induced CHF in the current analysis was higher compared with the incidence observed in the retrospective study by Von Hoff et al.,[1] supporting the contention of those authors that they may have underestimated the incidence. In addition, the current analysis indicates that CHF can and does occur at a total cumulative doxorubicin dose $\leq$ 300 mg/m^2, albeit infrequently. The estimated cumulative percentage of patients with doxorubicin-related CHF in the current analysis also was higher compared with the percentage reported by Von Hoff et al.[1] We observed an estimated cumulative percentage of 5% of patients at a cumulative dose of 400 mg/m^2, 26% of patients at 550 mg/m^2, and 48% of patients at 700 mg/m^2 compared with the estimated cumulative percentages of 3% of patients at 400 mg/m^2, 7% of patients at 550 mg/m^2, and 18% of patients at 700 mg/m^2 reported by Von Hoff et al.[1] To avoid the risk of attributing every event of CHF to doxorubicin exposure, an independent cardiologist was retained to review the potential doxorubicin-related CHF events; criteria included the total dose and clinical scenario of each patient. We believe that our estimate of doxorubicin-related CHF is accurate in that it neither underestimates the incidence (because we examined patients diligently for cardiovascular events) nor overestimates the incidence by attributing every event of CHF to doxorubicin exposure.

It should be noted that cyclophosphamide was used together with doxorubicin in the three studies evaluated. Although cyclophosphamide may augment the cardiotoxicity of doxorubicin, the effects at conventional doses usually are small and are unlikely to account for the substantial differences between our findings and the historic findings of Von Hoff et al.[1]

It also is possible that radiation played a role along with doxorubicin as a contributing factor to CHF. However, it is unlikely that radiation resulted in notable changes or may account for substantial decreases in systolic function for patients who experienced doxorubicin-related CHF, especially because only 10 of those 32 patients were exposed to radiation.

In their breast carcinoma study, Speyer et al.[6]

TABLE 5
Number of Patients at Risk and Number of Patients with On Study Cardiac Events, by Cumulative Dose

	No. of patients at risk/no. of events							
	Study 088001 (n = 348 patients, 87 events)		Study 088002 (n = 111 patients, 32 events)		Study 088006 (n = 171 patients, 30 events)		All studies (n = 630 patients, 149 events)	
Dose (mg/m^2)	At risk	Events	At risk	Events	At risk	Events	At risk	Events
50	313	2	97	0	150	0	560	2
100	309	0	93	1	150	0	552	1
150	306	11	92	12	150	10	548	33
200	245	2	67	3	115	1	427	6
250	234	2	62	1	110	1	406	4
300	219	20	58	4	103	7	380	31
350	85	2	29	1	34	0	148	3
400	81	16	21	4	28	3	130	23
450	52	6	13	1	21	0	86	7
500	40	12	10	3	16	2	66	17
550	20	7	5	0	11	2	36	9
600	9	1	5	1	7	2	21	4
650	7	3	1	0	5	1	13	4
700	3	1	1	0	3	1	7	2
750	2	0	1	0	2	0	5	0
800	2	1	1	0	0	0	3	1
850	1	1	1	1	0	0	2	2

evaluated the number of patients with decreases in LVEF in the placebo arm. Those authors found that a median of 4% of patients had a decrease in LVEF value in the doxorubicin dose range of 275–399 mg/m^2, and 15% of patients had a decrease in the dose range of 400–500 mg/m^2; a cumulative 28% of patients who received up to 500 mg/m^2 of doxorubicin had a decrease in LVEF value.[6] Our data indicate that an estimated 54% of patients who received doxorubicin at a cumulative dose of up to 500 mg/m^2 would have cardiac events. This estimate is not affected greatly by the inclusion of data from Study 088002 (the lung carcinoma trial), because, when data from Studies 088001 and 088006 were evaluated separately using the same criteria, 52% of patients were estimated to have cardiac events at a cumulative dose of 500 mg/m^2. Cardiac events were defined as one of three changes in LVEF values compared with baseline value as well as clinical CHF. Of the patients who had only decreases in LVEF, it is not known which patients would have developed CHF if they had received additional doxorubicin, nor is the extent of their cardiac damage known.

LVEF was measured by MUGA, which reportedly is a good predictor of CHF.[7] Therefore, we believed that we would be able to predict which individuals would be at risk of developing CHF through careful monitoring. However, the data presented in the current report indicate that LVEF may not be an accurate predictor of CHF. In fact, 21 of 32 patients who experienced CHF had a reduction $< 30\%$ in LVEF values from baseline values, which Schwartz et al. considered the cut-off level for increased risk of CHF.[7] Furthermore, in our study, similar LVEF changes occurred in many other patients who did not develop CHF. Thus, further investigation will be required to help predict whether a patient is at high risk for CHF. One recent study suggests that indices of early diastolic function, as determined by radionuclide angiocardiography, are predictive for the early detection of anthracycline-related cardiotoxicity.[8]

A promising test for anthracycline-induced cardiotoxicity is the evaluation of serum cardiac troponin T levels.[9] In pediatric patients who received anthracycline chemotherapy and underwent cardiovascular surgery, the magnitude of elevation of serum cardiac troponin T levels predicted left ventricular dilatation.[10] Any new assay for the prediction of doxorubicin-related CHF would need to be compared with the standard cardiac biopsy, which reportedly is highly sensitive in measuring cardiomyopathy.[11] Despite this high sensitivity, the use of cardiac biopsy is somewhat limited by its invasiveness.

The schedule of drug delivery may be an important factor in anthracycline-associated cardiotoxicity. Von Hoff et al. reported a significant difference in CHF

TABLE 6
Estimated Cumulative Percentage of Patients with On Study Cardiac Events, by Cumulative Dose

	Cumulative percentage and SE							
	Study 088001 (n = 348 patients, 87 events)		Study 088002 (n = 111 patients, 32 events)		Study 088006 (n = 171 patients, 30 events)		All studies (n = 630 patients, 149 events)	
Dose (mg/m^2)	%	SE	%	SE	%	SE	%	SE
50	0.6	0.4	0.0	—	0.0	—	0.4	0.3
100	0.6	0.4	1.1	1.1	0.0	—	0.5	0.3
150	4.2	1.1	14.0	3.6	6.7	2.0	6.5	1.0
200	5.0	1.3	17.8	4.1	7.5	2.2	7.8	1.2
250	5.8	1.4	19.2	4.2	8.3	2.3	8.8	1.2
300	14.4	2.2	24.7	4.8	14.6	3.1	16.2	1.7
350	16.4	2.6	27.3	5.2	14.6	3.1	17.9	1.9
400	32.9	4.2	41.2	7.5	23.7	5.7	32.4	3.2
450	40.7	4.8	45.7	8.2	23.7	5.7	37.9	3.5
500	58.5	5.4	62.0	9.7	33.2	8.1	53.9	4.2
550	73.0	5.7	62.0	9.7	45.4	10.2	65.4	4.6
600	76.0	5.8	69.6	11.3	61.0	11.8	72.0	4.8
650	86.3	5.6	69.6	11.3	68.8	11.8	80.6	4.9
700	90.9	5.3	69.6	11.3	79.2	11.6	86.2	4.8
750	90.9	5.3	69.6	11.3	79.2	11.6	86.2	4.8
800	95.4	4.2	69.6	11.3	—	—	90.8	4.9
850	100.0	—	100.0	—	—	—	100.0	—

SE: standard error.

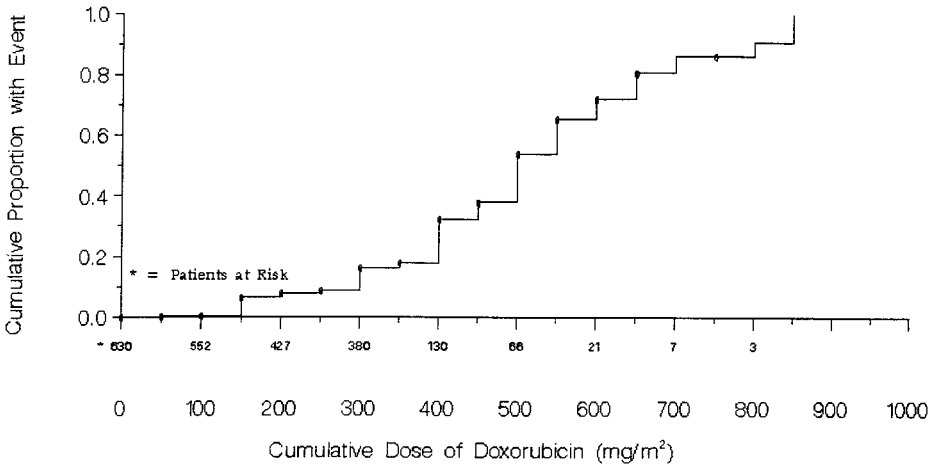

FIGURE 3. Cumulative doxorubicin dose at onset (on study) of doxorubicin-related cardiac events in 630 patients who were randomized to receive a doxorubicin-containing regimen plus placebo.

when comparing doxorubicin administration schedules.[1] Their results indicated that the lowest probability for developing CHF was found with the weekly schedule, compared with the schedule of three times per week repeated every 3 weeks or the schedule of once every 3 weeks.[1] Legha et al. studied continuous-infusion doxorubicin and found that endomyocardial biopsy changes were significantly less severe than in patients receiving bolus infusion.[12]

Reduction of the cardiotoxic profile of the anthracycline itself continues to be of interest. Epirubicin reportedly had lower cardiotoxicity compared with doxorubicin on the basis of a mg/m^2 cumulative dose.[13] In a large retrospective analysis, Ryberg et al. reported estimated CHF risks of 0.6% and 14.5% at cumulative doxorubicin doses of 550 mg/m^2 and 1000 mg/m^2, respectively.[14] However, a long-term prospective trial[15] showed that patients who received high cumulative doses of epirubicin (850–1000 mg/m^2) had a risk of CHF that increased over a 5-year period (11% at 1 year, 20% at 5 years). Liposomal anthracyclines seemed to have an improved cardiotoxicity profile in

preclinical studies.[16,17] Clinical and endomyocardial biopsy data suggest that cardiotoxicity may be less marked with liposomal anthracyclines compared with free anthracyclines.[18,19]

It is believed that the mechanism for doxorubicin-related cardiomyopathy is free-radical formation with subsequent lipid peroxidation.[20] DZR is an antioxidant that functions by chelating iron, thereby reducing iron dependent free-radical formation.[21] The development of DZR has had the important clinical effect of allowing the delivery of a higher cumulative dose of anthracycline to patients while reducing cardiotoxicity. In contrast, antioxidants that function after free radicals are formed, such as α-tocopherol and *N*-acetylcysteine, have not provided significant protection from anthracycline-induced cardiac damage.[22,23] However, further evaluation of probucol, which may prevent doxorubicin cardiotoxicity through its antioxidant activities,[24] may be warranted.

The risk of CHF for various subgroups within our study was interesting to note. Based on the generalized Wilcoxon test (which places greater emphasis on events that occur at lower cumulative doses), the difference in risk between older patients (age $>$ 65 years) and younger patients was not appreciable. However, the difference in risk between patients in these age groups was appreciable after a cumulative doxorubicin dose of 400 mg/m^2. This association of risk with age was also a finding of Von Hoff et al.[1] However, all comparisons between subgroups should be interpreted with caution because of the small number of events of CHF that occurred in some subgroups and because of the exploratory nature of these comparisons.

Patients in all three studies tended to have very advanced stages of disease, with associated comorbidities. Although it is possible that cardiotoxicity may be less frequent in healthier patients, our patient populations probably are a reasonable reflection of the types of patients who receive doxorubicin in current practice.

Patients were followed after their participation in the study, and this had an effect on the estimates of the cumulative percentages of patients with doxorubicin-related CHF. Because only 11 of 32 patients experienced on study CHF, if we had restricted our analyses to on study CHF, then our estimates would have been lower. However, not all patients were followed off study for an equal amount of time, and those patients who were censored after receiving open-label DZR had no off study follow-up data. Although an analysis could be undertaken using dose as a time dependent covariable to estimate the relative risk of doxorubicin-related CHF given a 50 mg increase in cumulative doxorubicin dose, it is unlikely that the relative risk is constant as the cumulative dose increases.

An analysis of prospective data from three Phase III trials indicates that doxorubicin-induced CHF occurs with greater frequency than reported previously. This conclusion has important implications for the monitoring and treatment of patients receiving anthracycline chemotherapy. Patients of advanced age may be at greater risk for CHF and may benefit from the early administration of a cardioprotectant or the use of doxorubicin as an infusion. We also conclude that LVEF is not a sensitive test for predicting CHF. It is critical both to identify an accurate means of predicting this serious side effect and to explore ways to reduce anthracycline-induced cardiotoxicity further. This may be accomplished through changes in both anthracycline administration schedules and formulations and by the use of cardioprotective drugs.

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