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ORIGINAL ARTICLE

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Doxorubicin-induced congestive heart failure in elderly patients with metastatic breast cancer, with long-term follow-up: the M.D. Anderson experience

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Abstract *Purpose*: Correlation between aging and doxorubicin-induced congestive heart failure in patients with metastatic breast cancer was studied to determine whether doxorubicin-induced congestive heart failure in elderly patients with metastatic breast cancer is a clinically significant issue. *Methods*: This was a retrospective study with a median follow-up of 16.8 years. The setting was a comprehensive cancer center in a large city. A group of 682 consecutive patients with metastatic breast cancer presented to The University of Texas M.D. Anderson Cancer Center between 1973 and 1980. All patients received doxorubicin by bolus infusion. Patients in group 1 ($n = 538$) were aged 50 to 64 years; patients in group 2 ($n = 144$) were aged 65 years and older. Medical records of all patients were reviewed. Patients who had congestive heart failure were identified and analyzed. The diagnosis of doxorubicin-induced congestive heart failure was made and confirmed by a cardiologist at the time of its development. The main outcome measure was the cumulative probability of developing doxorubicin-induced congestive heart failure in elderly patients with metastatic breast cancer compared to a younger age group. *Results*: In group 1, 33 patients, and in group 2, 13 patients developed doxorubicin-related congestive heart failure. The cumulative doses of doxorubicin administered to patients with congestive heart failure were 410 mg/m^2 (range 150–550 mg/m^2) and 400 (range 100–570 mg/m^2), respectively. The time interval from the last date of doxorubicin treatment to the development of congestive heart failure was, respectively, 5 months (range <1–65 months) and 9 months (range <1–28 months). There was no statistically significant difference between the two congestive heart failure subgroups, nor were we able to identify risk factors that could have increased the risk of congestive heart failure among these patients. *Conclusion*: Older patients with metastatic breast cancer and no significant comorbidity can be treated with doxorubicin-based chemotherapy with no added risk of developing congestive heart failure beyond that in the younger age group.

Key words Doxorubicin · Congestive heart failure · Metastatic breast cancer · Elderly

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Introduction

Doxorubicin has been shown to induce degenerative myocardial changes in both animal models and humans [1–6]. The occurrence of such changes is cumulative and dose-dependent [4, 6, 7]. Doxorubicin-induced cardiomyopathy may manifest as congestive heart failure (CHF) [1, 4, 8–13] during treatment or at various intervals of time from the last dose [8, 14]. Many risk factors have been shown to augment this phenomenon, including radiation therapy to the mediastinum [9, 11, 15–19], older patient age [15], preexisting cardiac conditions [11], hypertension [9], and other cardiotoxic chemotherapeutic agents [9, 10].

The incidence of CHF increases with age: according to the Framingham study [20], CHF developed in 9 of 1000 women aged between 65 and 94 years compared with 3 of 1000 women aged between 55 and 64 years. On the other hand, the incidence of coronary artery disease between the two groups are 11 and 17 per 100,000, respectively. In addition, the incidence of breast cancer increases sharply with age: 71.4 per 100 000 for women younger than 65 years versus 434.6 per 100 000 for

Table 1 Schema for diagnosis of doxorubicin-induced congestive heart failure (D-CHF)

D-CHF is characterized by:
Symptoms: dyspnea, orthopnea, paroxysmal nocturnal dyspnea, lower extremity edema, weight gain, weakness, dizziness
Signs: cool and clammy skin, edema, orthopnea, increased jugular venous distention, tender and enlarged liver with positive hepatojugular reflux, sinus tachycardia with summation gallop, pulsus alternans, displaced and sustained apical impulse with pansystolic murmur, basilar pulmonary rales, ascites, pleural effusion
Radiology: cardiomegaly, increased pulmonary vasculature or congestion, decreased left ventricular ejection fraction
Echocardiogram: decreased left ventricular ejection fraction
Absence of other etiologic factors: valvular heart disease; conduction abnormalities; ischemic heart disease; pericardial disease; hypertension; toxic, metabolic, infiltrative, hypertensive, or infectious cardiac diseases

women 65 years or older, according to the SEERS data [21]. Despite the risk of CHF, the value of doxorubicin-based regimens in the treatment of breast cancer is indisputable: It has been shown to reduce the risk of death when given in the adjuvant setting and perhaps to cure patients with metastatic disease [22–24]. Thus, the associated increase in the incidences of CHF and breast cancer with age necessitates the evaluation of the impact of doxorubicin-based therapy on the incidence of CHF among older women. We, therefore, retrospectively reviewed and compared The University of Texas M.D. Anderson Cancer Center experience of treating metastatic breast cancer with bolus doxorubicin in women aged $\geq$65 years versus those aged 50 to 64 years.

Patients and methods

Among 1581 consecutive patients with metastatic breast cancer referred to M.D. Anderson between 1973 and 1980, 682 patients aged 50 years and above were treated with front-line doxorubicin-based protocols after signing an informed consent [25–40]. After 1980 patients were predominantly treated with continuous infusion doxorubicin and were not included in this review. All protocols were approved by the institutional review board at M.D. Anderson Cancer Center. Doxorubicin was given by rapid intravenous infusion. Patients' records were divided into two groups: 538 women who were 50 to 64 years old (group 1), and 144 women who were 65 to 82 years old (group 2). All charts were reviewed, and patients' characteristics were collected, including: the Zubrod performance status; tumor burden [41]; history of chemotherapy or hormonal therapies, locoregional radiation therapy, hypertension, and various cardiac abnormalities; presence of diabetes; and abnormalities on the chest roentgenogram or electrocardiogram. Median follow-up, subsequent cardiotoxic chemotherapy, incidence of CHF, and time from the last date of doxorubicin treatment to the occurrence of CHF were recorded. Patients who presented with clinical evidence of CHF were evaluated by the Cardiology Service. Various etiologies of CHF were sought and excluded. Doxorubicin-induced CHF (D-CHF) was defined as the clinical symptoms and signs of CHF that the clinical investigator and the cardiology consultant who cared for the patient determined to result from doxorubicin administration. D-CHF was defined as pump failure in the absence of other causes such as ischemic, metabolic, hypertensive, or valvular heart disease (Table 1).

Treatment plan

All patients were treated with bolus doxorubicin-based protocols (Table 2). Patients with severe or uncontrolled comorbid conditions, including cardiovascular conditions, were excluded from the protocols; age was not an exclusion criterion. The doxorubicin-based regimens included either cyclophosphamide, fluorouracil, tegafur, or ifosfamide. Patients were allowed to receive total cumulative doses of 450 to 550 mg/m^2 of doxorubicin; subsequent chemotherapy consisted of CMF (cyclophosphamide, methotrexate, and fluorouracil), vinblastine, and/or mitomycin.

Endpoints and statistical analysis

The objective of this study was to determine whether elderly patients ($\geq$65 years) with metastatic breast cancer and receiving

Table 2 Distribution of patients by protocols (*A* doxorubicin, *BCG* bacillus Calmette-Guerin, *C* cyclophosphamide, C_p *Corynebacterium parvum*, *E* vitamin E, *F* fluorouracil, *Ft* Ftorafur, *Lv* levamisole, *M* methotrexate, *P* Peptichemio, *Ps* Pseudogen, *T* tamoxifen, *Th* thiotepa, *I* ifosfamide

Reference	Drugs	No. of Patients (CHF$^+$)	
		Age 50–64 years	Age ≥65 years
25	FAC	19 (2)	2 (–)
26, 27	FAC-BCG	97 (6)	29 (2)
28, 29	FAC-BCG-Lv	48 (1)	11 (–)
30	FAC-M	51 (–)	8 (2)
31	AC-Ft	43 (5)	12 (–)
28	FAC-Lv	53 (4)	13 (3)
32	FAI-BCG-Lv	17 (2)	2 (–)
33	FAC	7 (–)	–
Hortobagyi et al. (unpublished)	FAC-Cp	30 (3)	6 (–)
34	FAC-M-Cp-Ps	21 (2)	11 (–)
35	FAC-T	33 (2)	14 (1)
36	FAC	27 (2)	2 (1)
37	FAC-E	10 (1)	3 (–)
38	AC	14 (–)	4 (1)
39	FAC-P-Th	13 (1)	3 (–)
40	FAC-Ps-T	55 (2)	24 (3)
Total		538 (33)	144 (13)

Table 3 Patient characteristics of 682 patients with metastatic breast cancer (*NED* no evidence of disease, *WD* with disease)

	Group 1 (538 patients)	Group 2 (144 patients)
Race		
White	479 (89%)	123 (85%)
Black	37 (7%)	13 (9%)
Hispanic	20 (4%)	8 (6%)
Other	2 (< 1%)	–
Age (years)		
50–54	174 (26%)	–
55–59	184 (27%)	–
60–64	180 (26%)	–
65–69	–	94 (14%)
70–74	–	41 (6%)
>75	–	9 (1%)
Median Age (years)		
Median	57	68.5
Range	50–64	65–82
Zubrod performance status		
0–1	189 (35%)	45 (31%)
2	294 (55%)	77 (53%)
3–4	55 (10%)	22 (15%)
Cumulative doxorubicin (mg/m^2)		
Median	420	411
Range	12–1100	50–570
% of intended doxorubicin dose given		
Median	82.5	81
Range	25–170	50–110
Locoregional radiation therapy		
Yes	359 (67%)	97 (67%)
No	179 (33%)	47 (33%)
No. patients dead	532	144
No. patients alive (NED/WD)	6 (5/1)	0
Survival (months)		
Median	22.5	20.5
Range	1–244	1–123

Table 4 Characteristics of doxorubicin-related patients with congestive heart failure

	Group 1 Age 50–64 years (n = 33)	Group 2 Age 65+ years (n = 13)
Age (years)		
Median	58	68
Range	50–63	65–74
Performance status		
Median	1	1
Range	0–3	0–3
Cumulative doxorubicin (mg/m^2)		
Median	410	400
Range	150–550	100–570
% intended dose given		
Median	90	80
Range	60–100	75–100
Interval to CHF (months)		
Median	5	9
Range	< 1–65	< 1–28
Locoregional radiotherapy		
None	8 patients (24%)	5 patients (38%)
Left side	14 patients (42%)	5 patients (38%)
Right side	11 patients (33%)	3 patients (23%)
Other cardiotoxic drugs	19 patients (58%)	9 patients (69%)
History of hypertension	6 patients (18%)	4 patients (31%)

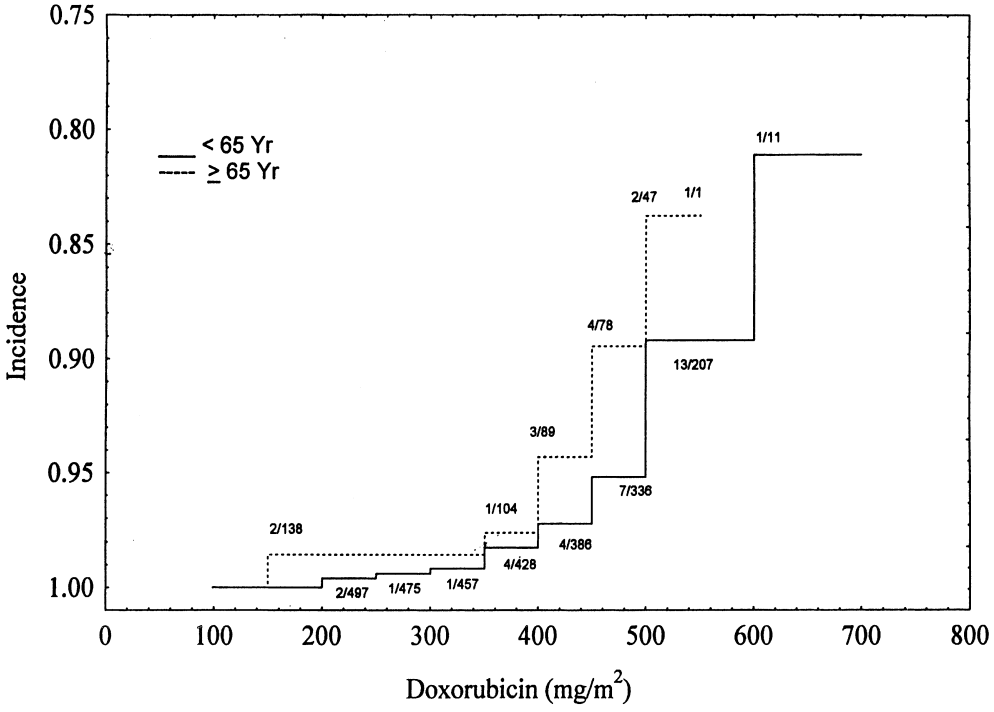

Fig. 1 Incidence of doxorubicin-associated congestive heart failure for patients <65 or ≥ 65 years

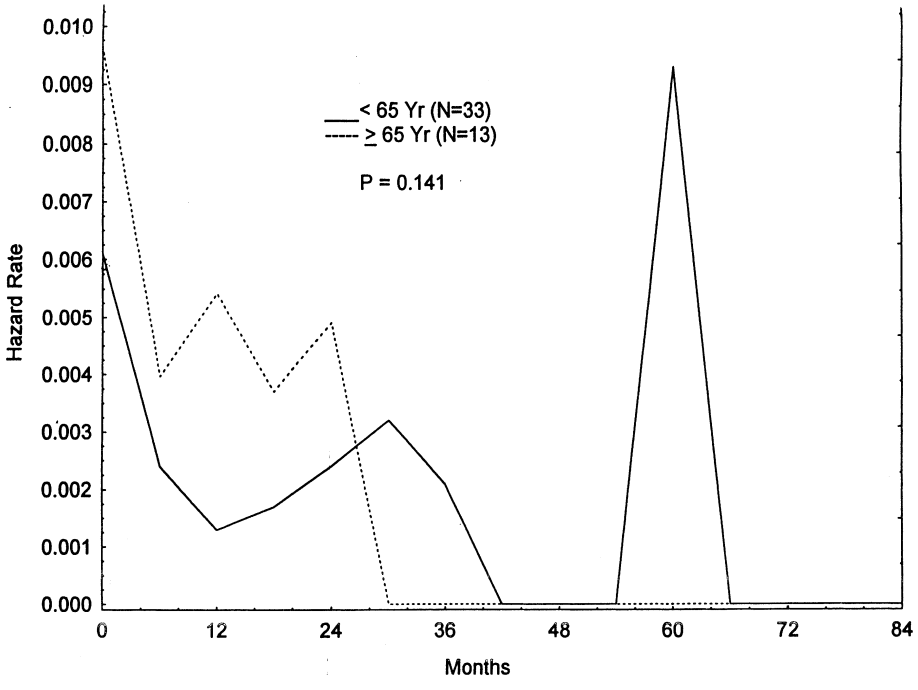

Fig. 2 Hazard rates for congestive heart failure from doxorubicin by age group

doxorubicin-based chemotherapy are at higher risk than their younger counterparts (50 to 64 years) of developing CHF. The cumulative probability of developing D-CHF was calculated for the two groups. The risk of D-CHF per unit time, as measured from the date of the last dose of doxorubicin, was calculated using the Cox regression model [42]. Tests between the groups studied were carried out using the Chi-squared test. A *P*-value of 0.01 or less was considered statistically significant and strong evidence against the null hypothesis.

Results

The patient characteristics in the two groups were similar, as shown in Table 3. The Zubrod performance status in the two groups was comparable, with a median of 2. All patients started chemotherapy at 100% of the planned dosage. The median follow-up period for sur-

Table 5 Cardiac disease profile of the younger group (group 1,538 patients) before and after doxorubicin-based treatment. *CAD-MI* coronary artery disease-myocardial infarction, *CHF-misc* doxorubicin-unrelated congestive heart failure, *D-CHF* doxorubicin-related congestive heart failure, *HTN* hypertension, *PE* pulmonary embolism

Cardiovascular disease	Baseline	Postchemotherapy cardiac status	
		Unchanged from baseline	Additional cardiac diagonses
None	442	406	20 (D-CHF) 1 (HTN) 1 (pericarditis) 1 (arrhythmia) 13 (CHF-misc)
Hypertension	72	54	10 (D-CHF) 5 (CHF-misc) 1 (PE) 1 (arrhythmia) 1 (CAD-MI)
Arrhythmia	6	6	–
Other[a]	18	15	3 (D-CHF)

[a] Palpitations, coronary artery disease, murmurs, pericardial effusion, valvular diseases

Table 6 Cardiac disease profile of the older patients (group 2, 144 patients) before and after doxorubicin-based treatment. *CAD-MI* coronary artery disease-myocardial infarction, *CHF-misc* doxorubicin-unrelated congestive heart failure, *D-CHF* doxorubicin-related congestive heart failure, *HTN* hypertension, *PE* pulmonary embolism

Cardiovascular disease	Baseline	Postchemotherapy cardiac status	
		Unchanged from baseline	Additional cardiac diagnoses
None	101	90	8 (D-CHF) 1 (arrhythmia) 1 (HTN) 1 (CAD-MI)
Hypertension	29	24	3 (D-CHF) 1 ("heart attack"[b]) 1 (CAD-ischemia) 1 (arrhythmia) 1 (CAD-MI)
Arrhythmia	2	2	–
Other[a]	13	8	3 (D-CHF) 1 (CAD-MI) 1 (arrhythmia)

[a] Palpitations, coronary artery disease, murmurs, pericardial effusion, valvular diseases
[b] No details available

viving patients was 201.5 months (range 163–218 months). In group 1, 359 patients (67%), and in group 2, 97 patients (69%) had received locoregional radiation therapy. Estimates of tumor burden were based on the number and area of metastatic disease sites [41]. There was no statistically significant difference in tumor burden, nor was there a difference in the distribution of the dominant metastatic sites.

The Quantile-Quantile plot of the cumulative doxorubicin given showed similar distributions for both age groups. CHF occurred in 66 patients (12%) in group 1 and in 22 (15%) in group 2. Among the entire group, 33 patients (6%) in group 1 and 13 (9%) in group 2 were confirmed to have D-CHF (Table 4). The total dose of doxorubicin administered among the 538 younger patients ranged from 12 to 1100 mg/m^2 (median 420 mg/m^2); among the 33 patients with D-CHF, the range was 150 to 550 mg/m^2 (median 410 mg/m^2, mean 375 mg/m^2), and the median total dose of doxorubicin received by patients who did not develop CHF was 430 mg/m^2. The total dose of doxorubicin administered among the 144 older patients ranged from 50 to 570 mg/m^2 (median 411 mg/m^2, mean 353 mg/m^2); among the 13 patients with D-CHF, the range was 100 to 570 mg/m^2 (median 400 mg/m^2), and the median total dose of doxorubicin received by patients who did not develop CHF was 410 mg/m^2. We were not able to show that locoregional radiotherapy, use of additional cardiotoxic drugs, or a history of hypertension would significantly increase the incidence of D-CHF among the older age group. The incidence of D-CHF was related to the total dose of drug administered. The cumulative probability of developing D-CHF in the younger group was 0.01 at 400 mg/m^2, 0.02 at 450 mg/m^2, 0.06 at 500 mg/m^2, and 0.09 at 600 mg/m^2. In patients older than 64 years, the cumulative probability of developing D-CHF was 0.03 at 400 mg/m^2, 0.05 at 450 mg/m^2, and 0.04 at 500 mg/m^2. The difference in the risk of developing D-CHF between the two groups did not reach statistical significance ($P = 0.1$; Fig. 1).

The median interval to the development of D-CHF from the last dose of doxorubicin was 5 months (range 1 to 65 months) for the younger group and 9 months (range 1 to 28 months) for the older group. The risk of D-CHF per unit of time from the date of the last dose of doxorubicin is shown in Fig. 2. In the younger group, most of the D-CHF conditions occurred within the first few months, but the risk remained for 5 years following the last dose of doxorubicin. In the older group, however, most of the D-CHF conditions occurred within the first 2 years after the last dose of doxorubicin, with no statistically significant difference between the two groups ($P = 0.14$). Tables 5 and 6 illustrate the various cardiovascular diagnoses encountered in the two age groups both before and after doxorubicin-based treatment.

Of the patients in the younger group who developed D-CHF, 25 had undergone locoregional radiotherapy, and 8 had not. In the older patient group, on the other hand, 8 patients who developed D-CHF had had locoregional radiotherapy, and 5 had not. In group 1, 14 patients, and in group 2, 5 patients, who developed D-CHF had had left locoregional radiotherapy. We found no statistically significant difference between the two D-CHF subgroups in terms of radiotherapy received.

In group 1, 19 D-CHF patients had subsequently received cyclophosphamide or mitomycin-C, which are cardiotoxic agents, and 9 patients in group 2 had

received such additional therapies. The administration of additional potentially cardiotoxic drugs did not significantly increase the occurrence of D-CHF ($P = 0.667$). A history of hypertension was documented in 6 (18%) of the patients in group 1 who developed D-CHF and in 4 (31%) of those in group 2 ($P = 0.430$).

Discussion

Doxorubicin-induced cardiotoxicity is a well-established phenomenon [43]. The administration of this drug by intravenous bolus is associated with a 2% to 16% incidence of CHF related to total cumulative dose [44–46]. The cumulative dose of doxorubicin is positively associated with the development of CHF: 1% in patients treated with up to 300 mg/m^2, 4% in patients treated with 450 mg/m^2, and up to 30% in patients treated with more than 550 mg/m^2 [45, 47–49]. Although doxorubicin-based regimens are well tolerated among elderly women with metastatic breast cancer [50], it has not been clear whether the use of doxorubicin boosts the natural incidence of CHF with increasing age.

Children, who have virtually no cardiac risk factors or comorbidity, are at a risk of developing doxorubicin-induced cardiomyopathy (3.9 to 23%) equivalent to or even slightly higher than that of adults [44, 51–53]. In addition, the interval from the end of treatment to the development of CHF may be very long in children (up to 18 years) compared with that in adults (< 36 months) [45, 51, 53]. This has been attributed to the inhibition of myocyte growth following doxorubicin therapy in children [54, 55]. Sustained subclinical cardiac damage, therefore, may be exacerbated by additional stress to the myocardium, such as intercurrent viral infection resulting in late-onset cardiac dysfunction [56]. With age, however, the susceptibility to cardiac diseases, particularly CHF, increases [20], probably due to increased cardiac wall stress [20]. Whether the increased incidence of CHF with age makes elderly patients particularly susceptible to the cardiomyopathic effects of doxorubicin needs critical assessment. We believe our analysis offers a reasonable start to understanding this issue by analyzing this set of data.

Our study was a retrospective review of all patients older than 49 years, chosen from a group of 1581 patients presenting to M.D. Anderson over a 7-year period with metastatic breast cancer and treated with intravenous bolus doxorubicin-based protocols. We analyzed the medical records of patients who developed CHF while receiving doxorubicin or at any time thereafter. The etiology of CHF was carefully assessed in each case, as shown in Table 2. Risk factors such as locoregional radiotherapy, other cardiotoxic drugs, or hypertension that may increase the risk of cardiac morbidity, were evaluated.

The development of D-CHF is dependent on the cumulative dose administered and the amount of time elapsed since the last treatment. We have shown that neither the probability nor the hazard rate of developing CHF with increasing cumulative doxorubicin administration, in the two groups, was statistically significantly different. Although we found a trend toward an increased incidence of D-CHF with increasing doses of doxorubicin in the two groups, the difference was too small to suggest that doxorubicin resulted in advancing the onset of CHF among older patients (i.e. exerted a lead-time effect), or that the cumulative amount of doxorubicin given lowered the threshold for developing CHF.

Our study detected an increase in the incidence of D-CHF in group 2 compared with group 1; however, it was of no statistical significance. Although a minor component of such an increase in the incidence of D-CHF could be attributed to the aging process [20], doxorubicin was not more detrimental to the older group; doxorubicin did not significantly add to the incidence of CHF or its mortality when compared to the younger group, nor did D-CHF adversely affect survival, because most of the affected patients died of progressive disease ($P = 0.222$; Table 7).

We have shown that elderly patients ($\geq$65 years) with metastatic breast cancer tolerate doxorubicin-based chemotherapy as well as patients who are 50 to 64 years of age. Although there is a well-recognized increase in the incidence of CHF with age, we found this increase to be similar in magnitude in the two groups studied. We also showed that in patients with metastatic breast cancer and no cardiac comorbidity, risk factors such as hypertension, radiotherapy, or the use of other cardiotoxic drugs did not further characterize patients who later developed CHF.

Several options can potentially help to reduce or prevent anthracycline-induced cardiotoxicity [57]. The incidence of D-CHF can be reduced by giving doxorubicin by a 48- to 96-h continuous infusion or by using cardioprotective agents (e.g. dexrazoxane) after giving bolus doxorubicin in excess of 300 mg/m^2. Therefore, elderly patients with no preexisting cardiac disease can be treated safely with doxorubicin-based chemotherapy and benefit from decreased risk of death from breast cancer in the adjuvant setting or achieve palliation and control of metastatic disease without a significantly increased risk of developing CHF over and beyond that encountered by the younger age group. D-CHF did not adversely affect survival; most of the affected patients died of progressive disease. This suggests that age did not significantly add to the incidence of CHF or its mortality among patients treated with doxorubicin. Therefore, a modest increase in

Table 7 Cause of death in patients who developed doxorubicin-induced congestive heart failure (*CHF*)

	Patients aged 50–64 years ($n = 33$)	Patients aged 65+ years ($n = 13$)	*P*-value
Progressive cancer	30 (91%)	11 (85%)	
CHF	1 (3%)	2 (15%)	0.222
Unknown	2 (6%)	–	

the incidence of D-CHF over the CHF that naturally occurs as patients age could be accepted in favor of controlling cancer-related morbidity with doxorubicin-based chemotherapy.

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