A Prospective Randomized Comparison of Epirubicin and Doxorubicin in Patients With Advanced Breast Cancer

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Fifty-four patients with advanced breast cancer who had failed prior nonanthracycline combination chemotherapy were randomized to treatment with either epirubicin 85 mg/m² or doxorubicin 60 mg/m² intravenously every three weeks. Of 52 evaluable patients, 25% (six of 24) treated with epirubicin, and 25% (seven of 28) treated with doxorubicin experienced major therapeutic responses. The median duration of response to epirubicin was 11.9 months compared to 7.1 months with doxorubicin. Cardiotoxicity was monitored by serial multigated radionuclide cineangiocardiography performed at rest and after exercise. Laboratory evidence of cardiotoxicity was defined as a decrease in resting left ventricular ejection fraction of > 10% from the baseline value, or a decrease of 5% or greater with exercise compared with the resting study performed on the same day. Fifteen patients treated with epirubicin and 18 patients treated with doxorubicin had at least two determinations of left ventricular ejection fraction and were evaluable for laboratory cardiotoxicity. Using methods of survival analysis, the median doses to the development of laboratory cardiotoxicity were estimated to be 935 mg/m² of epirubicin and 468 mg/m² of doxorubicin. Four patients treated with epirubicin and five treated with doxorubicin developed symptomatic congestive heart failure. The median cumulative dose at which congestive heart failure occurred was 1,134 mg/m² of epirubicin compared with 492 mg/m² of doxorubicin. Fewer episodes of nausea and vomiting were observed in patients receiving epirubicin. Epirubicin is a new anthracycline with reduced cardiac toxicity, but preserved efficacy in the treatment of patients with advanced breast cancer.
J Clin Oncol 3:818–826. © 1985 by American Society of Clinical Oncology.

DOXORUBICIN (DOX), or Adriamycin (Adria Laboratories, Columbus, Ohio), is one of the most useful antineoplastic agents available. It possesses a broad spectrum of clinical antitumor efficacy and is the most active nonhormonal drug for the treatment of breast cancer.[1,2] Its use, however, is limited by cumulative, dose-dependent, chronic cardiotoxicity. In retrospective studies, the incidence of symptomatic congestive heart failure (CHF) was estimated to be approximately 3% to 4% after a cumulative DOX dose of 450 mg/m² and 6% to 10% after 550 mg/m²; the incidence of CHF rises steeply after higher cumulative doses.[3–5] On the basis of these retrospective studies, an empiric dose limitation of 450 to 550 mg/m² has been recommended when DOX is used on a standard every three week schedule.[3,4]

More recently, however, subclinical cardiac injury has been documented at considerably lower doses. Cardiac monitoring with noninvasive techniques[6–8] and endomyocardial biopsy[8,9] identify patients being treated with DOX who have asymptomatic functional or morphologic cardiac abnormalities and who may be at high risk for the development of clinical congestive cardiomyopathy. Discontinuation of therapy in these patients may prevent cardiac failure, but also results in curtailment of the antineoplastic effect of DOX.

One approach to solving this problem is the development of DOX analogues that retain antineoplastic activity but possess reduced potential for cardiac damage. Preclinical studies suggest that this may be possible by structural alteration of the anthracyline molecule.[10] Epirubicin (4′-epi-doxorubicin, EPI) is one such compound. It is a stereoisomer of DOX in which the hydroxyl group at the 4′ position of the aminosugar side

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Submitted Aug 2, 1984; accepted Dec 17, 1984.

Supported in part by National Institutes of Health grant No. CA-05826 and by a grant from Farmitalia Carlo Erba, Milan, Italy.

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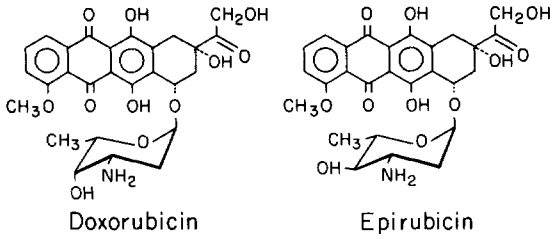

Fig 1. Structures of doxorubicin and epirubicin (4′-epi-doxorubicin).

chain is epimerized (Fig 1). The antitumor activity of EPI in animal models is similar to that of DOX, but EPI is a less toxic compound with regard to both cytotoxicity and cardiac injury.[10,11] In the mouse, EPI and DOX have similar patterns of distribution to various tissues, although drug levels are lower in heart and spleen with EPI.[12] Pharmacokinetic studies in tumor-bearing mice and rats[13] indicate that EPI is more extensively metabolized by liver than DOX. The two compounds have similar pharmacokinetic behavior in humans, although EPI is eliminated more rapidly.[14]

In two clinical phase I studies, EPI was found to have acceptable toxicity at doses of 85 to 90 mg/m^2 given intravenously (IV) every three weeks.[14,15] The acute toxicity was qualitatively similar to that seen with DOX. Therapeutic responses were observed in patients with advanced breast cancer in both studies.

Before an analogue of an active drug is accepted for clinical use, its toxicity and efficacy should be compared with that of the established compound. We used multigated radionuclide cineangiocardiography (RNCA) to assess cardiac toxicity in this prospective, randomized study comparing the efficacy, acute, and chronic toxicities of EPI with DOX in patients with advanced breast cancer.

MATERIALS AND METHODS

Patient Eligibility

This study was conducted in patients with advanced breast cancer who had progressed after receiving combination chemotherapy. Patients whose prior treatment included an anthracycline were excluded from this study. Other criteria for eligibility included a performance status of ≥ 50% (Karnofsky scale), a WBC count ≥ 4,000/μL, a platelet count ≥ 100,000/μL, normal serum bilirubin levels (< 1.5 mg/dL), and objectively evaluable or measurable disease. Patients with clinical evidence of active cardiac disease or a left ventricular ejection fraction (LVEF) of < 50% by RNCA were excluded.

Pretreatment Evaluation and Follow-up Studies

Pretreatment evaluation of patients included complete history and physical examination, complete blood cell count (CBC), 12-channel biochemical profile, serum creatinine, chest roentgenogram, ECG, and bone scan. Areas of increased uptake on bone scan were further studied with roentgenograms to determine the nature of the abnormalities. Liver scans were done only if there was elevation of the hepatic enzymes on the biochemical profile.

Blood counts were initially monitored weekly, and then less frequently after the pattern of myelosuppression was established. Biochemical profiles were repeated every six weeks. All evaluable or measurable parameters of disease were reevaluated at least every six weeks.

Study Design

After determining eligibility, informed consent was obtained. Patients were stratified for performance status (Karnofsky scale ≤ 70% *v* ≥ 80%) and for estrogen receptor status of the primary or a metastatic lesion (positive or unknown *v* negative). All patients were then randomly assigned to receive either EPI or DOX. Randomization was performed using the method of random permuted blocks, which assured an equal number of patients in each arm at specified time points.[16]

Treatment Protocol

EPI was supplied by Farmitalia Carlo Erba (Milan, Italy) in a powdered form that was reconstituted with sterile water for injection *United States Pharmacopeia*. DOX was prepared in accordance with the package insert. Both EPI and DOX were administered by slow (five minute) injections through an established IV line every three weeks. The dose of EPI was 85 mg/m^2, and the dose of DOX was 60 mg/m^2. It was anticipated that these doses would produce equivalent degrees of myelosuppression. Doses were adjusted based on the degree of myelosuppression observed using a predetermined schedule. Neither patients nor physicians were blinded with respect to treatment.

Evaluation of Response

The criteria for evaluation of therapeutic response were based on the recommendations of the Breast Cancer Task Force of the National Cancer Institute (Bethesda, Md).[17] These guidelines were modified to include a minor response (MR) category for those patients with unequivocal therapeutic responses, but less than that required for a partial response (PR). Any patient who developed progressive disease within three months of starting therapy was considered to have progressed even if she had demonstrated transient tumor regression. Duration of response was measured from the first day of initiation of therapy until progressive disease was documented.

Evaluation of Toxicity

The percent of projected dose received was calculated for each patient as the average of all doses the patient received (mg/m^2) ÷ 85 if the patient was randomized to EPI and ÷ 60 if the patient was randomized to DOX.

Cardiac toxicity was assessed in all patients by both clinical evaluation and RNCA. Clinical examination was performed prior to each dose of anthracycline. RNCA was done with the patients in supine position at rest and during maximum symp-

tom-limited bicycle exercise. Patients' RBCs were labeled in vivo by injecting 10 to 20 mCi of technetium 99m IV 30 minutes after stannous pyrophosphate injection. Images of the left ventricle were recorded by positioning the camera in the left anterior oblique position, using a computer-based procedure gated to the electrocardiogram. LVEF was determined by computer-assisted analysis of left ventricular time-activity curves. After images were obtained at rest for six minutes, supine bicycle exercise was started with graded increment in exercise load and monitoring of heart rate and blood pressure. Exercise was continued until the patient achieved the maximum predicted heart rate or until limited by fatigue, severe dyspnea, or chest pain. Imaging was obtained for three minutes at the point of maximal tolerable exercise. Both resting and, when the patient's condition permitted, stress RNCA were repeated after the first three doses, and after every other dose thereafter. In our laboratory, during the period of time that this study was conducted, the reproducibility of LVEF determination by RNCA was ± 5%. Therefore, for this study laboratory cardiac toxicity was defined as decrease in resting LVEF of > 10% from pretreatment baseline or a decrease in LVEF with stress of > 5% from the resting baseline obtained on the same day.

Antineoplastic therapy was discontinued if the LVEF decreased to < 40% or if the patient developed clinical congestive heart failure. In the case of DOX, at a cumulative dose of 550 mg/m^2 patients were offered the option to discontinue therapy or to continue with close monitoring of cardiac function with RNCA. No such dose limitation was imposed for patients on the EPI arm, as the toxic cumulative dose of EPI was not established at the onset of this study.

Statistical Methods

Comparison of response rates between the two arms was made using a chi-square test. Several other comparisons, such as percent of projected dose, used the two-sample Wilcoxon test.[18] Cumulative dose to cardiotoxicity and response durations were regarded as right censored variables, which were estimated using the method of Kaplan and Meier.[19] The log rank test[20] was then used to compare the cumulative dose to cardiotoxicity or the response durations between the two arms. All hypothesis tests were two-sided.

RESULTS

Patient Characteristics

A total of 54 women were randomized, 25 to the EPI arm and 29 to the DOX arm. The characteristics of the patients are presented in Table 1. Eight patients on the EPI arm and 14 on the DOX arm had received prior radiotherapy to the chest, mediastinum, or thoracic spine that may have exposed the myocardium to ionizing radiation. In addition, four patients who received EPI and six who received DOX had a history of well-controlled systemic arterial hypertension. Although all patients had received prior chemotherapy which included cyclophosphamide or other alkylating agent, no patient had been previously treated with mitomycin C. No patient was being treated with digitalis glycosides or antiarrhythmics.

Table 1. Characteristics of 54 Patients Randomized to Treatment With EPI or DOX

	Epirubicin	Doxorubicin
No. of patients	25	29
Median age (yr)	52	52
(Range)	(36–74)	(33–63)
Median performance status	80	80
(Range)	(50–100)	(50–100)
Estrogen receptor protein		
Positive	9	15
Negative	11	11
Unknown	5	3
Sites of disease		
Skin	10	13
Nodes	10	10
Lung, pleura	12	13
Liver	9	10
Bone	15	15
Brain	1	1
No. of metastatic sites		
One	8	9
Two	7	10
≥ Three	10	10

Dose Attenuation

The percent of projected dose received by patients in each arm was compared. Doses were reduced more frequently on the DOX arm as compared to the EPI arm, in which two patients' doses were escalated. The median actual dose administered was 100% of the projected dose of EPI and 86% of the planned dose of DOX (Wilcoxon test, $P = .01$).

Response Rates and Durations

Twenty-four patients on the EPI arm and 28 patients on the DOX arm are evaluable for therapeutic response (Table 2). The additional patient randomized to EPI died with progressive breast cancer and nadir sepsis 15 days after her first dose of EPI; she is excluded from analysis of therapeutic results, but is included in the analysis of hematologic toxicity. The inevaluable patient randomized to treatment with DOX refused to return for follow-up counts or further therapy, but was alive four months after her only dose of DOX; the patient is also excluded from analysis of hematologic toxicity.

Complete responses were not observed in ei-

Table 2. Therapeutic Responses

	Epirubicin	Doxorubicin
No. evaluable	24	28
Partial responses	6	7
Duration (mo)	(5, 8, 12, 13, 13, 14)	(4, 6, 6,* 7, 10, 10,* 13*)
Minor responses	1	7
Stable disease	8	7
Progression	9	7

*Therapy discontinued solely because of cardiac toxicity.

ther arm. Six (25%) of the 24 evaluable patients treated with EPI and seven (25%) of the 28 evaluable patients on the DOX arm achieved PRs. In addition, on the EPI arm, one patient experienced an MR and eight patients had stable disease. There were seven MRs on the DOX arm and seven patients with stable disease for at least three months. The median duration of PR for patients responding to EPI was 11.9 months, whereas median duration of PR on the DOX arm was 7.1 months. Although the major response rates did not differ between the two arms (chi-square test, $P = .98$), the difference in duration of response is of borderline significance (logrank test, $P = .11$). Cardiac toxicity alone did not limit the administration of EPI, but DOX was discontinued in three patients with ongoing PRs because of cardiac toxicity. Of the 13 patients with PRs, six had tumors that were estrogen receptor positive, six had estrogen receptor negative tumors, and in one patient the estrogen receptor value was unknown. There was no difference (log rank test, $P = .90$) in the median time to progression between the patients on the EPI arm (3.9 months) and those on the DOX arm (5.1 months).

Noncardiac Toxicity

Hematologic toxicity was similar in the two arms (Table 3). The median WBC nadir was 2.0 $\times$ $10^3/\mu L$ (range, 0.1 to 8.6) and the median platelet nadir was 132 $\times$ $10^3/\mu L$ (range, 20.0 to 279.0) in patients receiving EPI; the median WBC nadir was 1.8 $\times$ $10^3/\mu L$ (range, 0.3 to 6.9) and median platelet nadir was 130 $\times$ $10^3/\mu L$ (range 24.0 to 253.0) in patients on the DOX arm. One patient receiving EPI died of nadir sepsis. This patient had been extensively treated with radiation and chemotherapy before treatment on this protocol.

Other common toxicities included nausea, vomiting, and alopecia. Nausea or vomiting was documented in 58% of patients who received EPI and 67% of the patients who were treated with DOX. In general, the nausea and vomiting in patients on the EPI arm was less severe. Because all patients had been treated previously with chemotherapy, the degree and incidence of alopecia is difficult to assess; however, hair loss was noted in 50% of patients treated with EPI and 35% of those treated with DOX. Mucositis was observed in only 4% of patients on the EPI arm, and in 6% of patients receiving DOX.

Cardiac Toxicity

Each patient had a baseline RNCA scan, and in all patients the resting LVEF was > 50% with the exception of one patient in whom it was 48%. All patients are included in the analysis of cardiotoxicity. Fifteen patients on the EPI arm and 18 patients on the DOX arm had at least one follow-up RNCA and were evaluable for laboratory cardiotoxicity. The remaining patients did not have a repeat RNCA because of progressive disease before receiving three doses of anthracycline. Of the 15 evaluable patients treated with EPI, six had received prior radiotherapy to the chest wall, internal mammary lymph nodes, sternum, or thoracic spine prior to entry on this study, and two had a history of well-controlled mild hypertension. Of the 18 evaluable patients treated with DOX, seven had prior radiation exposure to the heart, two had hypertension, and two had both hypertension and prior radiotherapy.

Eight patients treated with EPI and nine patients treated with DOX had laboratory evidence

Table 3. Hematologic Toxicity

	No. of Patients	
	Epirubicin	Doxorubicin
Total	25	28
WBC nadir $\times$ 10^3		
≥4.0	2	1
3.0–3.9	1	5
2.0–2.9	10	4
1.0–1.9	7	13
<1.0	5	5
Platelet nadir $\times$ 10^3		
≥150.0	10	14
100.0–149.0	9	6
50.0–99.0	3	4
<50.0	3	4

of cardiotoxicity. The median cumulative dose to laboratory cardiotoxicity in these patients was 892 mg/m^2 of EPI and 360 mg/m^2 of DOX.

For all patients evaluable for cardiotoxicity by RNCA, laboratory cardiotoxicity data were further analyzed using methods of survival analysis. The median dose to development of cardiotoxicity for all evaluable patients was 935 mg/m^2 for EPI and 468 mg/m^2 for DOX (Fig 2A). The difference is highly significant (log rank test, $P < .0001$). These data were also analyzed taking into consideration the difference in myelosuppressive potency between the two drugs. As noted above, the doses of the drugs were adjusted to produce an equivalent degree of myelosuppression. Overall, 100% of the planned dose of EPI (85 mg/m^2) was administered; however, only 86% (52 mg/m^2) of the planned dose of DOX was given. Thus, all EPI doses were multiplied by 52/85 to compare the two drugs in equivalent units, and Kaplan-Meier estimates plotted (Fig 2B). The difference remains statistically significant with a P value of .04. Of the ten remaining patients on the EPI arm and eleven patients on the DOX arm who are not evaluable for laboratory cardiac toxicity because they did not have a second RNCA study, the total cumulative doses of EPI and DOX were not significantly different, whether or not myelosuppressive-equivalent doses were taken into consideration. Thus, even accounting for the difference in myelosuppressive potency, EPI is less cardiotoxic than DOX.

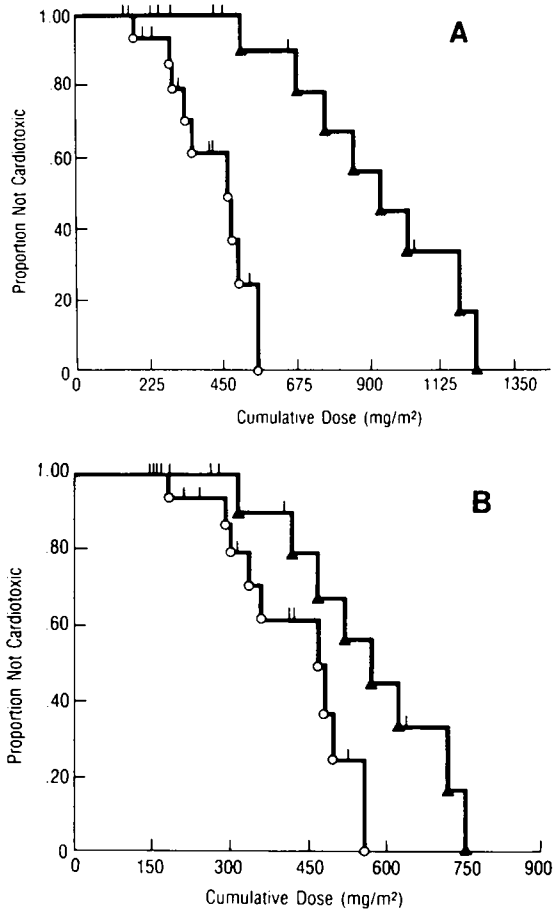

Fig 2. (A) Kaplan-Meier plots of cumulative doses of doxorubicin and epirubicin to the development of laboratory cardiotoxicity, ○ doxorubicin (18 patients/9 censored), ▲ epirubicin (15 patients/8 censored), (\|) indicates last follow-up. (B) Kaplan-Meier plots of cumulative doses of doxorubicin and epirubicin (expressed in doxorubicin-equivalent units) to the development of laboratory cardiotoxicity, ○ doxorubicin (18 patients/9 censored), ▲ epirubicin (15 patients/8 censored), (\|) indicates last follow-up.

A decrease in LVEF of > 5% with stress was not observed in the absence of a > 10% decrease in resting LVEF from baseline. Thus, for this patient population, the use of exercise did not appear to increase the sensitivity of the resting RNCA alone. Nor did all patients experience a steady progressive decline in LVEF; most maintained a stable LVEF until there was an acute decrease. This sometimes, but not always, occurred before the development of symptomatic congestive cardiomyopathy.

Four patients treated with EPI and five patients treated with DOX developed clinical congestive heart failure (CHF). The cumulative doses of EPI at which clinical CHF was observed (1,035, 1,105, 1,162, and 1,234 mg/m^2) were approximately twice the cumulative doses of DOX at which CHF was seen (456, 480, 492, 560, and 600 mg/m^2). One of the patients who developed CHF on the DOX arm is the patient who had the initial resting LVEF of 48%; this patient also had a history of pulmonary emboli and it was unclear whether this contributed to her cardiac decompensation. Six of 11 patients who received more than 450 mg/m^2 of DOX did not develop signs or symptoms of CHF. Of the patients who developed symptomatic CHF on the EPI arm, one had prior radiotherapy and one had hypertension. On the DOX arm, one of the patients who developed CHF had prior radiation exposure to the heart, one had hypertension, and one had prior radiotherapy as well as hypertension.

Survival analysis methods were also applied to

compare the cumulative doses to clinical CHF for patients in the two arms. There was a statistically significant greater cumulative dose to CHF for patients receiving EPI (log rank test, $P \leq .008$) with and without adjustment for the difference in myelosuppressive potency. Since only five patients treated with DOX and four treated with EPI actually developed clinical heart failure, this result should not be overinterpreted. Among patients who experienced clinical CHF, however, the median cumulative doses to CHF were 1,134 mg/m^2 of EPI and 492 mg/m^2 of DOX.

DISCUSSION

In this study, EPI had therapeutic activity in breast cancer similar to DOX, but produced less cardiotoxicity than the parent compound.

Long-term administration of DOX on a conventional every three week schedule is limited by the development of dose-related congestive cardiomyopathy. Although empiric dose restriction is widely practiced, many patients experience the onset of CHF before they receive 550 mg/m^2 of the drug. DOX cardiomyopathy has been reported in as many as 35% of patients who receive more than 550 mg/m^2 of the drug.[4] In a prospective adjuvant chemotherapy trial for patients with soft-tissue sarcomas, 14% of patients who received 430 to 600 mg/m^2 of DOX developed clinical CHF.[21] Thirteen percent of patients in another recent study developed CHF at a median dose of 405 mg/m^2 when DOX was given on an every three week schedule.[22] With optimal monitoring, one might be able to detect subclinical cardiac injury and prevent CHF by stopping the drug; this implies, however, the interruption of effective antineoplastic therapy.

Several approaches have been proposed to reduce the cardiotoxic effects of DOX. The use of potentially cardioprotective agents such as vitamin E,[23] *N*-acetylcysteine,[24] and ICRF-187[25] has been suggested, but the data have not been sufficiently promising to warrant large scale clinical trials. Recently, liposomal encapsulation of DOX has been shown to decrease the cardiotoxicity of DOX in experimental animals, although it is unknown whether the drug's antineoplastic effects are preserved.[26]

Modification of the traditional schedule of DOX administration has been advocated as a method to reduce cardiac injury. In nonrandomized trials, the use of a weekly DOX schedule has been reported to permit administration of a higher total dose of the drug.[27,28] Two recent studies that used endomyocardial biopsy have demonstrated that a larger total cumulative dose of DOX can be tolerated if the drug is given weekly[22] or by continuous intravenous infusion.[29] Such scheduling may be more costly than the conventional schedule, and may be inconvenient or impractical for both patients and physicians. Although the data are suggestive, it remains unproven that the antitumor activity of DOX is fully preserved when these schedules are used.

Development of less cardiotoxic, but equally efficacious, anthracylines is an alternative approach. Studies of structure-activity relationships demonstrate that changes at the 4′ position of the aminosugar moiety affect toxicity, and indicate that cardiotoxicity can be separated from therapeutic effect.[10] Structurally, EPI differs very slightly from DOX and has the same molecular weight, yet EPI and DOX have different therapeutic, myelosuppressive, and cardiotoxic potencies in animal systems.[11] This suggests that EPI might have a better therapeutic index in patients with cancer.

The optimal method for monitoring the cardiotoxic effects of anthracyclines is controversial. A combination of RNCA and endomyocardial biopsy is recommended for the individual patient at high risk for whom a therapeutic decision must be made.[30] However, RNCA alone has also been useful in studying anthracycline cardiotoxicity.[6,31] Although endomyocardial biopsy is probably the definitive measure of cardiac injury, RNCA has the advantage of being noninvasive and, therefore, acceptable to virtually all patients in a randomized study of antineoplastic agents. Potential selection factors that might bias the comparison of cardiac effects are thereby avoided.

In the present trial, EPI was compared with its parent compound in terms of both toxicity and antitumor efficacy. The observed major therapeutic response rate to EPI (25%) was identical to that observed with DOX (25%). This is similar to the 27% response rate reported by the Early Clinical Trials Group of the EORTC (European Organization for the Research on Treatment of Cancer).[32] It was also similar to the combined experience in the literature with DOX as a single

agent in previously treated women with breast cancer.[1]

The therapeutic index of an agent is defined by the relationship between the dosage required to produce therapeutic and toxic effects and by the magnitude of the favorable or unfavorable effects observed. On a molar basis, EPI was clearly less myelosuppressive than DOX; EPI was also less cardiotoxic. The difference in cardiac toxicity was manifested by the difference in total cumulative dose at which changes in LVEF occurred (Fig 2A), as well as by the difference in dose at which clinical CHF was seen (EPI, 1,035 to 1,234 mg/m^2 *v* DOX, 456 to 600 mg/m^2). Although these results could have been affected by the greater incidence of cardiac irradiation in patients treated with DOX, only three patients who had received such radiotherapy actually developed CHF, one on the EPI arm and two on the DOX arm.

Whether these findings reflect an improvement in therapeutic index is dependent on the two drugs' dose relationship for therapeutic effects. Expressed more plainly, is EPI a less cardiotoxic anthracycline, or merely a less potent anthracycline? In the murine tumor model systems, equal doses of EPI and DOX produce equal therapeutic effects with less host toxicity in the EPI-treated mice, but a clinical assessment can only be based on studies in humans. There are three prospective randomized comparison studies that address this issue in patients with breast cancer. In each study, the partial response rates of the EPI and DOX arms were equivalent. The design of these studies differed, however. In the present study, each drug was given every three weeks in doses that produced equivalent degrees of myelosuppression; a preplanned limitation on the total cumulative dose of EPI was not used. Brambilla and coworkers in Milan[33] studied equal doses (75 mg/m^2) of both drugs every three weeks; they limited the total cumulative dose of each drug to 600 mg/m^2. A third study[34] compared two multidrug combinations in which 5-fluorouracil (F) 500 mg/m^2 and cyclophosphamide (C) 500 mg/m^2 were combined with an equal dosage (50 mg/m^2) of either EPI (FEC [5-fluorouracil, EPI, cyclophosphamide]) or DOX (FAC) and administered every three weeks; the total dose of EPI was limited to 750 mg/m^2 and of DOX to 550 mg/m^2. In the Milan study, the complete plus partial response rate to EPI was 5/11 and to DOX, 7/15; FEC produced a major response rate of 45% compared to a 43% response rate to FAC.

The observations with regard to relative cardiac toxicity in the three studies provide internally consistent and complementary data. Since the present study did not use a fixed limitation for dose of EPI, patients who did not have progression of tumor were treated to the point of laboratory cardiotoxicity or clinical CHF; therefore, this study provides cumulative cardiotoxicity data that are not available in the other two studies. The other studies, which did use dose limits, provided data that could confirm the reliability of the survival analysis method we have used to assess the dose effect relationships with regard to RNCA changes.

In the present study, EPI was found to be significantly less cardiotoxic than DOX, even when the dose is normalized to full myelosuppressive equivalence. At cumulative EPI doses of 600 to 700 mg/m^2, two (13%) of the 15 evaluable patients at risk for RNCA changes developed a decrease in LVEF of $> 10\%$. In the other single agent study,[33] in which there was an empiric dose limitation of 600 mg/m^2, none of the seven EPI-treated patients who had RNCA experienced a decline in LVEF of $> 10\%$. In the multidrug study, no clinical cardiac dysfunction was seen in the EPI-containing (FEC) arm.[34]

In contrast, the present study predicts an incidence of laboratory cardiotoxicity in excess of 70% for those patients who receive more than 600 mg/m^2 of DOX. Although the numbers are small, in the Milan study three of five patients treated with DOX in whom RNCA was performed showed a decrease in LVEF of more than 10% (375, 450, and 525 mg/m^2).[33] In the multidrug study, therapy was discontinued in seven patients on the DOX-containing (FAC) arm because of cardiac dysfunction, including three with heart failure.[34]

The relatively good cardiac tolerance of EPI observed in the present breast cancer study has been confirmed in our extended phase II experience in other disorders. Most patients in our trials received less than 550 mg/m^2 of EPI; however, in 11 patients receiving cumulative EPI doses from 550 to 1,465 mg/m^2, RNCA abnormalities were observed in only four patients at 970, 1,180, 1,190, and 1,465 mg/m^2, respectively (C.W.

Young, unpublished data, January, 1985, New York).

Recently, the relative cardiotoxicity of EPI and DOX has also been examined by Torti and colleagues using endomyocardial biopsy.[35] Although the patients studied were heterogeneous, the data were subjected to multivariate analysis with regard to dose, prior cardiac irradiation, and schedule of drug administration. Assuming equal therapeutic potency, this analysis indicated that every three week EPI is less cardiotoxic than every three week DOX ($P = .0005$) and borderline less toxic than weekly DOX ($P = .06$).

In the present study, RNCA abnormalities correlated well with the presence of symptomatic heart failure. Although at times a decrease in LVEF was observed immediately before the development of CHF, we were unable to confirm the previously described pattern of predictable progressive decline in LVEF over time for all patients.[6] Many patients maintained their left ventricular function at the baseline value until it worsened abruptly shortly before or at the time that clinical CHF was observed. The sudden onset of clinical deterioration was also reported by Bristow who considered this a manifestation of a nonlinear relationship between myocardial structure and function.[36] Likewise, changes in LVEF in response to stress frequently accompanied a decline in LVEF, but we did not observe such a decline without a concommittant change in resting LVEF. Thus, while assessment of LVEF by RNCA was useful in quantitating changes in cardiac function for the purposes of this study, it cannot be recommended for routine monitoring of individual patients as a predictor of impending cardiac failure.

Our results show that EPI has therapeutic activity that is similar to that of DOX in patients with advanced breast cancer, and that EPI is a less cardiotoxic drug than DOX, even accounting for the difference in myelosuppressive potency. In this study, worsening cardiac function forced the premature discontinuation of DOX therapy in three patients experiencing partial responses, whereas effective treatment with EPI was never discontinued because of cardiac toxicity.

These findings, which are supported by the independent work of several other investigators,[32,33] provide encouragement for further clinical trials with EPI. Just as schedule modification has reduced the cardiotoxic effects of DOX,[22] exploration of a weekly schedule of EPI administration is warranted. In addition, the preliminary results from the FEC *v* FAC combination chemotherapy trial[34] suggest that EPI should be studied further in combination with other active agents in patients with advanced breast cancer.

ADDENDUM

Since this manuscript was prepared for publication, an additional patient treated with DOX developed clinical congestive heart failure in the postoperative period following exploratory laparotomy. This patient had shown a decrease in left ventricular ejection fraction and was included in the analysis of laboratory cardiac toxicity. She developed evidence of laboratory cardiotoxicity after a cumulative dose of 615 mg/m^2 of DOX. No further DOX was administered before her development of clinical congestive heart failure.

ACKNOWLEDGMENT

The authors wish to thank Dr Janet Wittes for her assistance in planning this trial, and Virginia Raymond, BSN, for assistance with analysis of the data.

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