A Phase II Trial of High Dose Epirubicin in Patients with Advanced Breast Carcinoma

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Supported in part by the Walther Cancer Institute.

Dr. Einhorn was supported by National Cancer Institute Grant 2R35CA39844-14.

This trial was supported by Pharmacia-Upjohn.

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Received May 10, 1999; revision received September 24, 1999; accepted September 24, 1999.

BACKGROUND. Anthracyclines are among the most active drugs in the treatment of breast carcinoma and exhibit a steep dose-response curve in vitro. This trial was performed to determine the efficacy and toxicity of epirubicin in the treatment of patients with advanced breast carcinoma when administered as a single agent in maximal doses.

METHODS. Patients with chemotherapy-naïve American Joint Committee on Cancer/International Union Against Cancer Stage IIIB or IV breast carcinoma received epirubicin, 180 mg/m^2, intravenously every 3 weeks for a maximum of 8 cycles of therapy. Hematopoietic growth factors and cardioprotective agents were not used routinely.

RESULTS. Twenty-seven patients were entered in the study. Although NCI/CTC criteria Grade 4 neutropenia occurred in 96% of patients, epirubicin was administered at 83.1% of the planned dose intensity. The median fall in left ventricular ejection fraction was 10%; clinical cardiac toxicity was observed in 3 patients. Objective responses were observed in 21 patients, including 6 complete responses.

CONCLUSIONS. High dose epirubicin was found to result in substantial hematologic toxicity but was highly active in the treatment of patients with advanced breast carcinoma. ***Cancer* 2000;88:375–80.** *© 2000 American Cancer Society.*

KEYWORDS: breast carcinoma, metastatic, chemotherapy, epirubicin, dose intensity, anthracycline.

Metastatic breast carcinoma, predicted to account for 43,900 deaths in 1998, represents a common cause of morbidity and mortality for women in the U.S.[1] Combination chemotherapy has represented the standard of care for women with steroid –receptor negative or hormone-refractory advanced disease for the past three decades. Such therapy frequently involves the use of $\geq$ 3 drugs and regularly results in response rates in the range of 30–60%, with a median duration of response of 6–12 months in previously untreated patients.[2] The impact of combination therapy on overall survival remains open to debate, although long term disease free survival is rare regardless of initial response.[3]

The rationale for combination chemotherapy has been that drugs with nonoverlapping toxicity and differing mechanisms of action may have additive, and possibly synergistic, activity against resistant clonal populations of tumor cells with only a minimal increase in toxicity. In reality, the use of chemotherapeutic agents in combination frequently necessitates reductions in the dose intensity of the most active individual agents. Because steep dose-response relations have been demonstrated in many preclinical studies, such dose reductions may negate the proposed benefits of combination therapy.

Alternatively, these dose-response relations may be exploited by using single agents at maximal tolerated doses.

Dose intensity with classic alkylating agents such as cyclophosphamide has been limited by the development of myelodysplastic syndromes or acute leukemia.[4] The anthracyclines represent another class of drugs for which a steep dose-response relation has been suggested. Superior response rates have been obtained with doxorubicin given in higher doses, with an 85% objective response rate reported in 1 study.[5] However, the use of high dose doxorubicin is limited by cumulative cardiac toxicity. Epirubicin, an analogue of doxorubicin, results in less cardiac toxicity at doses with equivalent hematologic effects.[6-8] Therefore epirubicin appears better suited to dose intensification. This Phase II study examined the efficacy and toxicity of epirubicin when administered as a single agent in maximal doses.

MATERIALS AND METHODS

Patients were eligible for the current study if they presented with advanced (Stage IIIB or IV by standard American Joint Committee on Cancer/International Union Against Cancer staging criteria),[9] histologically proven steroid–receptor negative or hormone-refractory breast carcinoma and had not previously received chemotherapy for their advanced disease. Prior hormonal therapy for metastatic disease was allowed. Adjuvant chemotherapy with a nonanthracycline-containing regimen was allowed if therapy was completed at least 6 months prior to study entry. Patients were required to have adequate renal, hepatic, hematologic, and cardiac function. Informed consent was obtained prior to treatment.

Patients were treated with epirubicin, 180 mg/m^2 intravenously, every 3 weeks. Patients with prior radiation therapy to bone marrow-containing areas received an initial dose of 135 mg/m^2. The epirubicin dose was reduced 15% when Grade 3-4 stomatitis occurred. If neutropenic fever, infection, or bleeding occurred in association with myelosuppression, treatment was withheld until toxicity resolved (Grade 0). Once resolution occurred, treatment resumed with a 25% dose reduction. Treatment was delayed until the granulocyte count was $> 1500/mm^3$ and the platelet count was $> 90{,}000/mm^3$. Patients requiring a treatment delay received a dose reduction for subsequent courses of therapy based on the degree of residual myelosuppression on Day 22. A 15% dose reduction was stipulated if the granulocyte count was $< 1000/mm^3$ and/or the platelet count was $< 50{,}000/mm^3$ and a 25% dose reduction was stipulated if the granulocyte count was $< 500/mm^3$ and/or the platelet count was $< 25{,}000/mm^3$. There were no dose escalations. Stimulators of hematopoiesis (e.g., granulocyte-colony stimulating factor and granulocyte-macrophage–colony stimulating factor) were not employed routinely.

Therapy was administered for a maximum of eight cycles of therapy, or until patients experienced progressive disease. Assessment of response, time to progression, and duration of survival were performed according to World Health Organization criteria.[10] Delivered dose intensity was calculated prospectively for each cycle of therapy by dividing the actual dose per day by the planned mg/m^2/day (8.571). Therapy was discontinued for a significant decrease in cardiac function as evidenced by a decrease in left ventricular ejection fraction (LVEF) by multigated blood pool (MUGA) scanning of $> 15\%$ from baseline or to 10% below the institutional normal, or the development of clinical congestive heart failure.

History and physical examination, complete blood count, and serum chemistries were performed prior to each course of therapy. Cardiac toxicity was evaluated by sequential MUGA scans performed before the fourth and eighth courses of therapy. Assessment of response was required prior to each cycle of therapy if tumor measurements could be performed by physical examination or chest radiograph. If measurement of tumor response was required, computed tomography was performed after the third and seventh courses of therapy.

RESULTS

From March 1989 to October 1991, 27 patients with advanced breast carcinoma (4 patients with Stage IIIB disease and 23 patients with Stage IV disease) were entered in this trial at Indiana University. Initial patient characteristics are shown in Table 1. Although patients generally had a good Karnofsky performance status, the majority of Stage IV patients (70%) had multiple sites of disease.

Patients received a median of six cycles of therapy. Myelosuppression was considered dose-limiting (Table 2). Of the eight patients who completed the full course of eight cycles of therapy, only two were able to sustain the initial dosage level. Dose reductions were required for 19 of the 26 patients who received > 1 epirubicin treatment; 5 patients required > 1 dose reduction. Overall, epirubicin was administered at 83.1% of planned dose intensity. An infection or neutropenic fever complicated 26 of 158 cycles of therapy (16%) and clearly was related to dose intensity. Of 92 cycles, 21 (23%) administered at the planned 180 mg/m^2 dose level resulted in neutropenic fever or infection compared with only 5 of 66 cycles (8%) ad-

TABLE 1
Patient Characteristics (n = 27)

Median age (yrs) (range)	55 (30–70)
Median KPS (range)	90% (60–100)
Prior adjuvant chemotherapy	6
Prior radiotherapy	13
Sites of disease	
Breast	4
Soft tissue	16
Bone	10
Liver	8
Lung	6
Pleura	4
Multiple sites	16
ER status	
Positive	9
Negative	10
Unknown	8

KPS: Karnofsky performance status; ER: estrogen receptor.

TABLE 2
Incidence Rate of Hematologic Toxicities[a]

	AGC (%)	Platelets (%)
Grade 1	0 (0)	3 (11)
Grade 2	0 (0)	10 (37)
Grade 3	1 (4)	1 (4)
Grade 4	26 (96)	7 (26)

AGC: absolute granulocyte count.
[a] Worst grade experienced per patient.

ministered at lower doses. No patient died as a result of infectious complications. Eight patients required red blood cell transfusions; two patients required platelet transfusions. Stomatitis and alopecia were the most frequent and severe nonhematologic toxicities (Table 3). Nausea occurred frequently but generally was well controlled.

Therapy was discontinued in 6 patients due to a decline in LVEF of $\geq$ 15% (range, 18–31%) according to protocol criteria. Nonetheless, clinical cardiac toxicity was observed in only three patients. One patient developed irreversible congestive heart failure 3 months after completion of epirubicin therapy to a total dose of 1160 mg/m^2 but died of progressive pulmonary metastasis. One patient had acute, reversible cardiomyopathy characterized by a high output failure syndrome after her first cycle of therapy. This patient subsequently was treated with weekly doxorubicin without further complications. One patient had a hypotensive episode of unclear etiology after her first cycle of therapy. The median fall in LVEF as measured by MUGA scan in all treated patients was 10% (range, +3–40%).

TABLE 3
Nonhematologic, Noncardiac Toxicities[a]

Toxicity	Grade 2 (%)	Grade 3 (%)	Grade 4 (5)
Stomatitis	8 (30)	10 (37)	1 (4)
Esophagitis	0 (0)	5 (19)	0 (0)
Dysphasia	0 (0)	2 (7)	0 (0)
Nausea	15 (56)	2 (7)	1 (4)
Emesis	15 (56)	1 (4)	1 (4)
Anorexia	10 (37)	0 (0)	2 (7)
Diarrhea	4 (15)	0 (0)	0 (0)
Alopecia	21 (78)	2 (7)	1 (4)
Radiation recall reaction	1 (4)	1 (4)	0 (0)
Phlebitis	5 (19)	0 (0)	1 (4)
Fever	12 (44)	5 (19)	1 (4)
Infection	10 (37)	2 (7)	0 (0)
Sepsis	0 (0)	5 (19)	2 (7)
Hemorrhage	0 (0)	0 (0)	1 (4)
Neurotoxicity	4 (15)	1 (4)	0 (0)
Fatigue/malaise	10 (37)	3 (11)	1 (4)
Cardiac function	2 (7)[b]	2 (7)	1 (4)

[a] Worst grade experienced per patient. All other toxicities $\leq$ Grade 1 in severity.
[b] Cardiac toxicity discussed in more detail in text. One patient with Grade 1 cardiac toxicity (asymptomatic decrease in left ventricular ejection fraction of 18%) was removed from the study according to protocol.

Objective responses were observed in 21 patients (78%), including 6 complete responses. Only two patients had progressive disease. The overall response rates (complete response plus partial response) of patients with Stage IIIB and Stage IV disease were similar, although all complete remissions occurred in patients with Stage IV disease. The median duration of response was 7 months (range, 1–15+ months) with a median overall survival of 19 months (range, 3–45 months).

DISCUSSION

This Phase II trial was performed prior to the routine use of hematopoietic growth factors or the advent of the cardioprotectant dexrazoxane. As expected, myelosuppression was severe. The majority of patients were not able to continue treatment at a dose of 180 mg/m^2. Although cardiac toxicity did not appear to limit dose intensity in the current study, a decline in LVEF was at least partly responsible for the discontinuation of treatment in six patients. Dexrazoxane has since been shown to decrease the rate of incidence of epirubicin cardiac toxicity without compromising response rates and may have allowed treatment to continue in responding patients.[11,12]

The importance of dose intensity in the treatment of metastatic breast carcinoma has been the subject of considerable debate since Hryniuk and Bush first published the concept of calculated dose intensity in

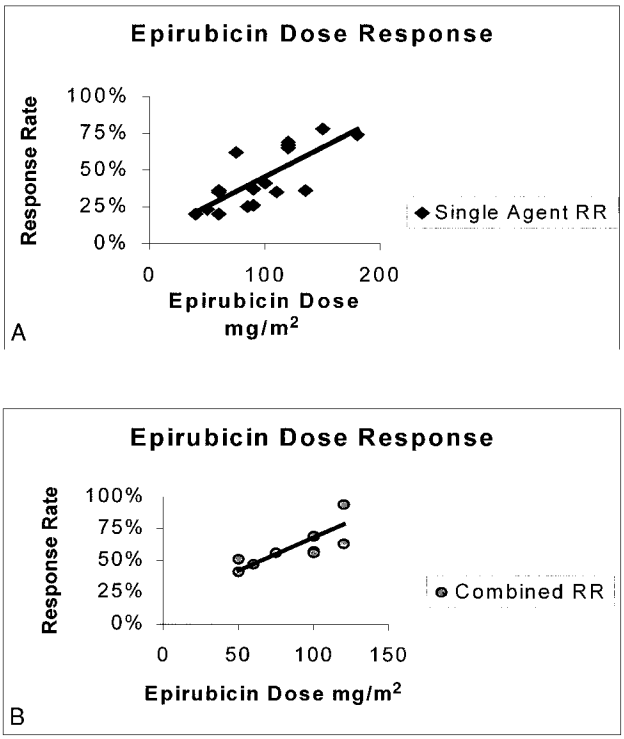

FIGURE 1. Epirubicin dose response relations. (A) Single agent response rates (RR) with epirubicin. Data from references 14–16 and 26–33. (B) RRs with various doses of epirubicin in combination with other agents. Data from references 17–19 and 34–37.

1984.[13] Using retrospective data from previously reported trials, their analysis suggested a dose-response relation for methotrexate-containing and doxorubicin-containing regimens. Several investigators have evaluated the role of epirubicin dose intensity either as a single agent or in combination with other cytotoxics for the treatment of patients with metastatic breast carcinoma. Although individual studies have not uniformly found increased response rates with higher doses, a review of these studies using the methodology of Hrynuik and Bush does suggest improved results with higher dose therapy, at least up to approximately 100 mg/m^2 (Fig. 1). Habeshaw et al. randomized 211 patients to received epirubicin at doses of either 50 mg/m^2 or 100 mg/m^2 every 3 weeks. Responses were observed in 22% of patients in the low dose group compared with 40% of patients in the high dose group ($P = 0.005$) although no improvement was noted in time to progression or overall survival.[14] In a small nonrandomized study, doubling the epirubicin dose from 60 mg/m^2 to 120 mg/m^2 provided a similar increase in objective response without prolongation of survival.[15] Bastholt et al. found convincing evidence of an epirubicin threshold dose near 90 mg/m^2 below which response rates and time to progression were inferior. Further escalation beyond 90 mg/m^2 did not appear to increase response rates or the duration of response, although 25% of patients who experienced disease progression with lower dose epirubicin regimens responded to retreatment at 135 mg/m^2.[16]

Epirubicin commonly has been combined with cyclophosphamide and 5-fluorouracil. Increasing the dose of epirubicin from 50 mg/m^2 to 100 mg/m^2 per cycle consistently has obtained more objective responses without uniform improvement in the duration of response or survival.[17,18] Comparable results were observed with the combination of epirubicin and cyclophosphamide alone.[19] Lalisang et al. achieved increased dose intensity (as calculated by dose/m^2/week) by shortening the treatment interval with fixed doses of epirubicin and cyclophosphamide rather than by escalating doses on a standard 3-week treatment schedule. Despite the differences in calculated dose intensity, little change in response parameters were observed between these strategies.[20]

The value of anthracycline dose intensity in adjuvant therapy remains uncertain. Hyrnuik et al. have extended their original analysis to combination regimens using widely different drugs.[21] The unit dose intensity (UDI) required to produce an arbitrary response rate of 30% was calculated from single agent, first-line trials of commonly used drugs. A summation dose intensity (SDI) was calculated for each regimen by expressing the dose of individual drugs as a fraction of its unique UDI and adding the resulting fractions to achieve a total score. In the analysis by Hryniuk et al. adjuvant trials with a difference in SDI of < 0.65 uniformly failed to find improvement with the higher dose regimens. A recently reported Cancer and Leukemia Group B-led intergroup adjuvant trial found no improvement in either disease free survival or overall survival with increasing doxorubicin dose in lymph node positive patients despite a difference in SDI of 0.8 from the standard to highest dose arms.[22] The intergroup trial was reported with a median follow-up of 22 months; however, we believe a longer period of observation is required before firm conclusions can be drawn. To our knowledge the only published trial of epirubicin dose intensity in adjuvant therapy altered both the dose intensity and duration of therapy; results favored the lower dose but longer treatment arm.[23]

Retrospective analyses of dose intensity have been criticized as merely a method to generate hypotheses.[24] Although intriguing, we agree that retrospective analyses cannot provide 'proof of principle' and should not substitute for well designed, prospective, randomized trials. The trials reviewed earlier do provide clear caution against needless dose reduction

because doses < 90 mg/m^2 consistently result in inferior response rates. Although this Phase II trial clearly demonstrates the significant single agent activity of high dose epirubicin in patients with metastatic breast carcinoma, it cannot speak to the ultimate value of dose intensity.

Epirubicin clearly is among the most active single agents in the treatment of patients with advanced breast carcinoma. This trial demonstrates the possibility of epirubicin dose escalation beyond standard levels in patients with metastatic breast carcinoma, with response rates similar to those observed with active combination regimens. The duration of response also compares favorably with that reported with the combination of doxorubicin and paclitaxel in a recently completed Eastern Cooperative Oncology Group trial.[25] Single agent epirubicin is a reasonable alternative to combination therapy in the initial treatment of patients with metastatic breast carcinoma.

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