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A phase II study of epirubicin in breast cancer

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We evaluated the efficacy of epirubicin in a phase II trial in breast cancer, as well as its cardiac toxicity. The study was carried out on 40 female patients with advanced, metastatic, or recurrent breast cancer. The patients were grouped into two groups: group I received 30 mg/m² epirubicin weekly, and group II 90 mg/m² epirubicin every 3 weeks. Cardiac monitoring was by ECG, röntgenography, echocardiography and endomyocardial biopsies. Clinical results were 35.3% overall response in group I, and 50% overall response in group II. No untoward cardiac toxicities were encountered. We conclude that epirubicin is an effective agent in breast cancer with relatively little cardiac toxicity.

Key words: Anthracyclines, breast cancer, epirubicin, phase II study.

Introduction

Anthracyclines play a major role in cancer chemotherapy in general, and breast cancer in particular.[1,2] Unfortunately their use has shown toxicities in the form of hemopoietic suppression, gastro-intestinal manifestations, and alopecia, as well as a unique cardiotoxicity manifested by dilated cardiomyopathy.[3]

Several approaches have been used to reduce the incidence of the cardiac toxicity of the anthracycline drugs. These include dose limitation, close cardiac monitoring (particularly in patients with risk factors), alteration of dosage schedules, administration of protective agents, and the development of new anthracycline analogs that retain chemotherapeutic efficacy, but have reduced cardiac toxicity.[4]

Initial animal studies[5] and human studies indicate that epirubicin (4′-epi-doxorubicin) is less cardiotoxic than doxorubicin, but is an effective antineoplastic agent.[6]

The aim of the present work is to study the effect of epirubicin and to evaluate its cardiac toxicity in breast cancer patients.

Materials and methods

All patients were females with advanced, metastatic, and/or recurrent breast cancer, pathologically proven. No patient had previously received either chemotherapy with an anthracycline agent or irradiation to the chest or mediastinum. At the time of entry into the study, no patient had evidence of heart disease or of hepatic or renal failure. All had a performance status between 1 and 3, according to the World Health Organisation scale.[7] All patients were subjected to a thorough clinical examination including history of the disease. Investigations included the following laboratory tests: complete blood picture, platelets, blood urea, serum creatinine, SGOT, SGPT, alkaline phosphatase and serum bilirubin. All these were carried out before initiation of therapy, and monthly thereafter. Radiography included skeletal survey, abdominal and pelvic sonography.

Epirubicin was injected slowly in a freely running intravenous solution of normal saline or dextrose in water. Treatment cycles were delayed for a leucocyte count of <3000/ml, or platelet count of $<100\,000$/ml. In patients with elevated serum bilirubin levels, the epirubicin dose was decreased by 50% for levels between 1 and 3 mg, and delayed for levels exceeding 3 mg.

Cardiac monitoring was in the form of a 12-lead ECG performed on every patient prior to initiation

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of therapy and before each additional dose. Posteroanterior and lateral roentgenograms of the chest and m-mode echocardiograms were performed before entry to the study, after its conclusion, and as needed according to the patient's condition.

Right-sided cardiac catheterization and right ventricular endomyocardial biopsies were obtained using the Cordis (Miami) biotome.[8] Three to five specimens were obtained from every patient, and prepared for examination by electron microscopy.

Patients were randomized into two groups. Group I received epirubicin at a dose of 30 mg/m^2 weekly for at least 2 months. Group II received epirubicin at a dose of 90 mg/m^2 every 3 weeks for at least four courses or as long as they were responding.

Results

Group I comprised 20 female patients. Age range was 30–60 years, mean 43 years. There were 13 pre-menopausal and 7 post-menopausal patients. Lesions were local in 14 cases, nodal in 14, hepatic 6, pulmonary 3, skeletal 2, and other breast 3 cases. Lesions were in two or more sites in all patients. The number of courses received ranged between 4 and 16 courses, mean 7. Three patients received two courses only and 50 were considered non-evaluable. Amongst 17 evaluable cases there was complete remission in one patient, partial remission in five, stable disease in seven, and increasing disease in four patients. The overall response was 6/17 (35.3%). Duration of response was 3–6 months, median 5 months.

Group II comprised 20 female patients. Age range was 32–59 years, mean 46 years. There were 15 pre-menopausal and 5 post-menopausal patients. Lesions were local in 14 cases, nodal in 15, hepatic in 6, pulmonary in 5, skeletal in one patient, and 3 in the other breast. All patients had two or more lesions. The number of courses given every 3 weeks was 3–10, mean 5 courses. Responses achieved were: complete remission in one patient, partial remission in nine, stable disease in three, and increasing disease in seven patients. The overall response was 10/20 (50%). Duration of responses was 3–10 months, median 7 months.

In both groups, responses were noted in visceral as well as local and nodal lesions. Thus, 7/12 patients with hepatic lesions attained remission; one complete and six partial remission. So visceral lesions responses were 14/22 (63%). The local lesions and the other breast lesions showed responses in 14/34 lesions. The nodal lesions showed partial responses in 12/29 lesions. None of the skeletal lesions showed any response.

Toxicities in both groups were: leucopenia Grades 1–2 in 50% of cases, alopecia Grades 1–3 in 100%, and gastro-intestinal Grades 1–2 in 100% of cases. As regards cardiac toxicities, the total cumulative doses of epirubicin given ranged from 180 to 918 g/m^2. No patients developed symptoms or signs of overt congestive heart failure at any stage of therapy. The mean resting heart rate before treatment was 88 ± 9 beats/minute and 93 ± 12 beats/minute after treatment. The mean systemic arterial pressure was 122/77 + 11/6 mm Hg after treatment.

Though these changes are all statistically significant, no correlation could be demonstrated between the change in these parameters and total dose, changes in hemodynamic or pathologic findings ($p > 0.1$ with each parameter). However, systemic hypertension was found several months after discontinuing epirubicin administration (due to progression of malignancy) in one patient who was under hormonal therapy at the time. All patients had normal resting ECG prior to epirubicin therapy. No change was noted after therapy in the mean calculated sum of the QRS voltage in the six standard limb leads of the ECG.

In most patients, technical difficulties were encountered in the form of inadequate acoustic window, narrowing of intercostal spaces in patients with liver enlargement, and fungating tumor masses on the left chest wall which precluded placement of the echo transducer in the proper position. In the five patients on whom echocardiography was carried out, the mean left ventricular percent fractional shortening showed no significant change.[8]

Endomyocardial biopsies were examined by light microscopy and electron microscopy. On light microscopy, myofibrillar loss of severity 1–2 was evident in two specimens: myocyte hypertrophy and myofibrillar disarray were not seen in any specimen. None showed severe vacuolization.

The electron microscopic findings showed myofibrillar lysis in three specimens, of severity 1–3. Dilatation of sarcoplasmic reticulum was noted in four specimens, mild in three specimens and moderate in one. Mitochondrial changes were noted in three specimens; these mitochondria were of abnormal shapes and sizes and showed degenerative changes and loss of cristae. Abnormally small mitochondria were often seen. Adipose tissue cells

were abundantly present in two biopsies. When the specimens were graded according to the Billingham scale,[9] two had a score of one, and three had a score of two. A strong correlation was found between the total dose per square meter of epirubicin and biopsy score ($r = 0.7$, $p = 0.0006$). When the patients were grouped according to the total cumulative dose per square meter body surface area, it was noted that patients receiving doses less than 450 mg/m^2 had biopsy scores of more than 1.5; namely, two. A cut-off point beyond which a change in the pathology score was more likely, was statistically defined to be at 900 mg/m^2.

Discussion

Anthracycline cardiotoxicity is usually expressed by the typical picture of congestive heart failure, which may be delayed for several months.[10] Epirubicin has been found to cause lower cardiac toxicity than doxorubicin in experimental animals,[11] and in patients.[12] Our patients did not develop anthracycline-related cardiac toxicity, such as rhythm disturbances, pericarditis/myocarditis syndrome, myocardial infarction, cardiogenic shock, sudden cardiac arrest, endomyocardial disease, or a change in the mean QRS voltage of the standard ECG leads. The cardiac size in chest röntgenograms did not change in any of our patients after conclusion of therapy.[8] Echocardiographic studies showed no significant change in the mean value of percentage fraction shortening before and after epirubicin therapy. Electron microscopy of biopsies from the five patients showed changes from mild to moderate severity, related to total cumulative dose of epirubicin.

In our study, we identified, through statistical analysis, a turning point beyond which there was a probability of change in pathologic scores at 450 mg/m^2 of epirubicin, indicating the need for cardiac monitoring of patients exceeding this dose. However, severe hemodynamic and pathologic changes were not seen, compared to doxorubicin given at a maximum cumulative dose of 550 mg/m^2. Bristow *et al.*[13] reported that the probability of an abnormal pathology score (>2) is increased at doses beyond 550 mg/m^2 of doxorubicin.

The present study results prove the efficacy of epirubicin in treating breast cancer using the weekly dose or the three-weekly dose. Results achieved were 35.3% overall response and 50% overall response, respectively. There was a statistical difference in favor of the three-weekly schedule. Furthermore, the median duration of response (7 months) was also better in the 3-week schedule. The most important point derived from this study was that response was noted in visceral lesions, especially the pulmonary lesions. Amongst 10 patients with pulmonary metastases, one achieved complete remission, and six achieved partial remission (70% overall response). The hepatic lesions (12 patients) showed partial remission in seven patients (58%). The responses were less marked in soft tissue and nodal lesions, and there were no responses in skeletal lesions. These results point to epirubicin as a good weapon in breast cancer patients with visceral metastases.

Our results are in agreement with other results from various investigators. Using a dose of 75 mg/m^2 epirubicin in advanced breast cancer, Bonadonna *et al.*[14] achieved a 62% overall response (median duration 7 months, range 5–12 months). Visceral lesions responded in 57% of cases. At a dose of 75 mg/m^2 every 3 weeks, the response rate achieved was 54% in a study by Armand *et al.*[15] in patients with breast cancer without prior chemotherapy. In a multi-institutional trial including six institutions, comparing epirubicin (90 mg/m^2) to doxorubicin, the median duration of response was 38.5 weeks and 24 weeks respectively.[16] Monochemotherapy trials with epirubicin as a weekly dose (25 mg/m^2 weekly) yielded an overall response of 38%.[17]

We can conclude that epirubicin is an effective chemotherapeutic agent in breast cancer with relatively few hematologic, gastro-intestinal and cardiac toxicities.

References

1. Young RC, Ozols RF, Myers CE. The anthracycline antineoplastic drugs. *N Engl J Med* 1981; **305**: 139–53.
2. Casazza AM. Antitumour activity of anthracyclines: experimental studies. In: Muggia FM, Young CW, Carter SK, eds. *Anthracyclines: antibiotics in cancer therapy*. Boston: Martins Nijhoff, 1982: 13–29.
3. Myers CE, Kinsella TJ. Cardiac and pulmonary toxicity. In: Devita, Hellmann, Rosenberg, eds. *Cancer, Principles and Practice of Oncology*, 2 edn. Philadelphia: Lippincott, 1985: 2022–32.
4. Weiss RS, Clagett-Carr K, Russo M, *et al.* Anthracycline analogs: the past, present, and future. *Cancer Chemother Pharmacol* 1985; **18**: 186–97.
5. Casazza AM, Guilliani FC. Preclinical properties of epirubicin. In: Bonadonna G, ed. *Advances in Anthracycline Chemotherapy: Epirubicin*. Milan: Masson, 1984: 31–40.
6. Bonfante V, Villani F, Bonadonna G. Toxic and therapeutic activity of 4'-epi-doxorubicin. *Tumori* 1982; **68**: 105–11.

7. Miller AB, Hoogstraten B, Staquet M, *et al.* Reporting results of cancer treatment. *Cancer* 1981; **47**: 207–9.
8. Dardir MD, Ferrans VJ, Michael YS, *et al.* Cardiac morphology and functional changes induced by Epirubicin chemotherapy. *J Clin Oncol* 1989; **7**: 947–58.
9. Billingham ME. Morphologic changes in drug induced heart disease. In: Bristow MR ed. *Drug-induced Heart Disease.* Amsterdam: Elsevier, 1980: 138–40.
10. Von Hoff DD, Layard MW, Basa P, *et al.* Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979; **91**: 710–7.
11. Ganzina F. 4'-Epi-doxorubicin, a new analogue of doxorubicin: A preliminary overview of preclinical and clinical data. *Cancer Treat Rev* 1983; **10**: 1–22.
12. Jain KK, Casper ES, Geller NL, *et al.* Aprospective randomized comparison of epirubicin and doxorubicin in patients with advanced breast cancer. *J Clin Oncol* 1985; **3**: 818–26.
13. Bristow MR, Billingham ME, Masson JW, *et al.* Clinical spectrum of anthracycline antibiotic cardiotoxicity. *Cancer Treat Rep* 1978; **62**: 873–4.
14. Bonadonna G, Brambilla A, Rossi A, *et al.* Epirubicin in advanced breast cancer. The experience of Milan Cancer Institute. In: Bonadonna G, ed. *Advances in Anthracycline Chemotherapy—Epirubicin.* Milan: Masson, 1984; 63–70.
15. Armand JP. Phase II and phase III studies with epirubicin in breast cancer in France. In: *Advances in Anthracycline Chemotherapy—Epirubicin.* Milan: Masson, 1984; 75–82.
16. Van Oostrum AT, Mouridsen J, Wilders J, *et al.* Doxorubicin versus epirubicin: a preliminary report of an on-going randomized phase II–III study in pretreated breast cancer patients. In: Bonadonna G, ed. *Advances in Anthracycline Chemotherapy: Epirubicin.* Milan: Masson 1984; 83–9.
17. Barni S, Tancini G, Paolorossi F, *et al.* A weekly schedule of epirubicin in pretreated metastatic breast cancer. *Proc Am Soc Clin Oncol* 1989; **29**: 109 (Abstract).

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