Myocardial Cytoprotection by Trimetazidine Against Anthracycline-Induced Cardiotoxicity in Anticancer Chemotherapy

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The ability of trimetazidine (2,3,4, trimethoxybenzylpiperazine dihydrochloride, TMZ) to protect the myocardium against anthracycline (ANT)-induced cardiotoxicity during chemotherapy has been evaluated in female patients with breast cancer. A clinical trial was conducted in 61 patients subdivided into three groups: group 1 (n = 15, G1) treated with standard ANT protocol and cardioprotection by dexrazoxane (DEX) plus TMZ (60 mg, daily dose); group 2 (n = 22, G2) treated with ANT and cardioprotection by TMZ only; and group 3 (n = 24, G3) scheduled to receive ANT therapy and DEX. All the patients submitted to an echocardiographic evaluation of diastolic function (E wave velocity, A wave velocity, isovolumetric relaxation time [IVRT], deceleration time [DT]) at enrollment (T0), at T1 time, at T2 time, and at T3 time. After a 12-month follow-up period, the patients showed a good conservation of diastolic function both in G1 and G2 groups. No statistically significant difference was observed in E wave and A wave velocity and E/A ratio after ANT treatment. TMZ produced a cardioprotective effect, comparable to DEX protection, against subacute and chronic subclinical cardiotoxicity with no significant changes in diastolic function after 1 year of follow-up.

Introduction

Trimetazidine (TMZ) increases cell tolerance to ischemia by maintaining cellular homeostasis.[1] In vitro and ex vivo reports have demonstrated that TMZ limits intracellular acidosis, inhibits sodium and calcium accumulation, maintains intracellular adenosine triphosphate levels, reduces creatine-phosphokinase release, preserves mitochondrial functions, reduces myocardial fatty acid metabolism, increases myocardial glucose metabolism, protects against oxygen free-radical–induced membrane damage,[2] and inhibits neutrophil infiltration. In clinical settings TMZ

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has shown antiischemic activity in stable angina and in chronic exertional angina.[3-5] A validated cardioprotective effect has been documented during coronary artery bypass graft surgery, in the reduction of myocardial infarct size,[6] in the myocardial protection during percutaneous transluminal coronary angioplasty,[7] and in the improvement of the contractile response of hibernating myocardium to low-dose dobutamine in ischemic cardiomyopathy.[8] These data suggest an antiischemic role of TMZ in myocardial protection and a preventive activity against ischemic left ventricular dysfunction.[9]

Anthracycline Cardiotoxicity

The anthracyclines (ANT; doxorubicin [DOX] and epirubicin [EPI]) are polycyclic, aromatic, red-pigmented antibiotics (rhodomycins) isolated from the soil actinomycete *Streptomyces.* The antineoplastic effect of the anthracyclines results primarily from intercalation into the deoxyribonucleic acid (DNA) of actively cycling cells, with blockage of DNA synthesis and subsequent cell death.[10] The inhibition of topoisomerase II, provided by TMZ, seems to be important in myocardial cytoprotection in a clinical setting. The most important toxicity limiting the clinical use of anthracyclines is cardiac.[11] Acute cardiac effects are noted within hours or a few days after bolus administration and consist primarily of cardiac arrhythmias (supraventricular tachycardia), ST-T wave changes, decrease in voltage, T wave flattening, and atrial end ventricular ectopies. Subacute effects are noted within days or weeks of administration and consist of toxic myocarditis or pericarditis (rare) principally documented with daunorubicin.[12] Chronic consequences are observed after weeks or months and consist of a cumulative dose-related myocardial cell damage (cardiomyopathy) that may finally culminate in congestive heart failure. DOX cardiotoxicity (congestive heart failure [CHF]) is low for a cumulative dose of 550 mg/m^2 (1%), with a sensible increase up to 30% for DOX cumulative dose of 800 mg/m^2. Whereas the incidence of cardiotoxicity (CHF) is low (1%) for a cumulative dose of 550 mg/m^2 of DOX, the incidence rises significantly (30%) with cumulative doses of 800 mg/m^2 of DOX. Epirubicin (EPI) cardiotoxicity seems to be less important until a cumulative dose of 1000 mg/m^2. Usually, the cardiac failure is left ventricular or biventricular; however, a selective right heart dysfunction has been reported. ANT-induced congestive heart failure carries a very poor prognosis and is lethal in 27% to 60% of cases.[13,14] For these reasons, regular follow-up of the patients should be considered. Cardiac function should be assessed at 3 and 12 months in all patients submitted to ANT therapy. Thus, the introduction of cardioprotective agents is now common to reduce the adverse consequences of chemotherapy. Dexrazoxane (DEX) is an analogue of ethylenediaminetetraacetic acid that probably acts by chelating iron, thus preventing the generation of ANT-induced oxygen free radicals. Previous randomized trials have demonstrated that DEX provides clinically significant cardioprotection against DOX[15] and EPI[16] cardiotoxicity. A DEX/EPI 6:1 and DEX/DOX 10:1 dose/ratio are now used in anticancer chemotherapy as an effective myocardial cytoprotection. Other recent observations[17] indicate that DEX is able to ameliorate DOX and EPI-induced cardiotoxicity in neoplastic patients, but no evidence of a similar cardioprotective effect sustained by TMZ are actually indicated in literature. The aim of this study was to furnish comparative data about cytoprotection by TMZ in comparison with DEX during ANT chemotherapy in female patients with breast cancer.

Methods

Patients

From March 1998 to July 2000, 112 patients with non-metastatic breast cancer entered the study (Table I). Eligibility criteria included histologically confirmed carcinoma, age 75 years or less, World Health Organization performance status 3 or less, measurable or assessable disease, adequate bone marrow, normal renal and liver function, and resting left ventricular ejection fraction 50% or greater. Patients were not included in the study if they had congestive heart failure, diabetes mellitus, arterial hypertension, baseline ejection fraction less than 50%, angina pectoris, prior myocardial infarction, history of other neoplasms, central nervous system involvement, previous exposure to ANT, and previous radiation therapy on the mediastinal area. All patients were to receive TMZ, 60 mg/day (oral administration) plus DEX 100 mg/m^2 (intravenous infusion)

Table I. Patient characteristics.

Parameter	G1	G2	G3	Total	f	p Value
Entered	36	38	38	112	–	–
Assessable	15	22	24	61	–	–
Age (yr)	55.87 ±12.44	61.86 ±10.09	47.25 ±12.31	56.15 ±12.29	15.1	0.000
Median (yr)	61.00	60.00	47.50	59.50	–	–
Body mass index (kg/m^2)	26.28 ±4.17	26.77 ±3.28	24.26 ±2.62	26.10 ±3.72	5.79	0.004
Body surface area (dm^2)	176.53 ±19.65	169.71 ±12.88	164.50 ±9.04	172.85 ±16.97	6.45	0.002
WHO performance status (mean)	1.34	1.45	1.43	1.38	999.9	0.000
Prior adjuvant CMF	–	–	–	–	–	–
Prior adjuvant hormonal therapy	–	–	–	–	–	–
Prior adjuvant radiotherapy	–	–	–	–	–	–
Acoustic window not adequate (n)	1	1	1	3	–	–
Deceased	5	3	5	13	–	–
Drop-out	8	8	9	35	–	–
Follow-up	15	7	4	33	–	–

CMF = cardiac monitoring follow-up.

(G1); TMZ alone, 60 mg/day (G2); or DEX alone, 100 mg/m^2 (G3) (Table II). The study was approved by local ethical committee and the patients gave written informed consent.

Follow-up Studies

Pretreatment evaluation included clinical history, physical examination, biochemical profile, chest radiograph, liver ultrasound or computed tomography, and bone scan. Blood counts and biochemical profile were obtained at T0 and repeated every 3 weeks or when appropriate. DOX and EPI cardiotoxicity was evaluated at T1, T2, and T3 (Table III) to evaluate ANT subacute and chronic effects. Cardiotoxicity was monitored by patient questionnaires, biochemical analysis, and clinical evaluations. Chemotherapy regimen, dosage adjustments, and planned evaluation time were assessed according to standard chemotherapy protocols.

Echocardiographic Monitoring

A complete Doppler-echocardiographic examination was performed by a Hewlett-Packard Sonos 5500 system. All patients were examined in partial lateral position by 3 different cardiologists unaware of clinical data. At least 3 consecutive cardiac cycles were considered[18]; cavity diameters and parietal thickness were obtained in M-mode on 2-dimensional frames according to American Society of Echocardiography recommendations. Parasternal long and short axis and apical 2- and 4-chamber views were used for the standard echocardiographic study. Left ventricular systolic performance was evaluated as follows: distance between the E point and the interventricular sep-

Table II. Study protocol.

Parameter	G1	G2	G3
Median no. cycles	6	6	6
Median EPI dose (mg/m^2)	960	960	960
Patients by cumulative EPI dose (mg/m^2)	10	7	7
<480 (mg/m^2)	–	–	–
480–640	–	–	–
641–960	5	4	4
961–1280	5	3	3
Median DOX dose (mg/m^2)	180	180	180
Patients by cumulative DOX dose (mg/m^2)	11	14	11
40–60	1	–	–
100–120	4	7	2
150–180	6	7	9
200–240	–	–	–
TMZ mean dose (mg)	58.34 ±7.56	57.65 ±6.45	–
DEX mean dose (mg/m^2)	1318.17 ±376.25	–	1289.34 ±477.11
DEX/EPI ratio	6:1	–	6:1
DEX/DOX ratio	10:1	–	10:1
Time of T1 (days)	73.40 ±41.43	55.20 ±14.14	52.50 ±28.72
Time of T2 (days)	172.12 ±12.78	183.21 ±56.12	135.32 ±21.21
Time of T3 (days)	355.71 ±36.45	390.12 ±48.56	368.23 ±38.22

DEX = dexrazoxane; DOX = doxorubicin; EPI = epirubicin.

tum, with fractional shortening (calculated in the short-axis projection), and by the ejection fraction, obtained by Simpson's rule modified evaluated in B-mode examination. In the presence of transmitralic flow pattern doubtful for pseudonormality, a complete evaluation of the diastolic function was assisted by a complete pulmonary venous flow study. Exclusion criteria eliminate all the clinical conditions imitating a diastolic dysfunction.[19-21] Left ventricular diastolic function was studied in apical projection with the sample volume between the tips of the mitral leaflets, in quiet expiration. Peak filling velocity (E-wave), peak telediastolic velocity (A-wave), and E/A ratio were obtained. Deceleration time (DT) was calculated from the interval between the E-peak and the point where the E-wave slope intercepts the baseline. Isovolumetric relaxation time

Table III. Cardiotoxicity evaluation.

Parameter	T0	T1	T2	T3	f	p Value
G1, n = 15						
E wave velocity (cm/sec)	66.14 ±16.34	71.23 ±16.43	58.71 ±23.34	69.84 ±22.91	1.17	0.328
A wave velocity (cm/sec)	70.14 ±19.73	75.91 ±13.51	67.73 ±15.76	78.20 ±12.19	1.48	0.231
E\A ratio	1.00 ±0.33	0.96 ±0.27	0.98 ±0.49	0.96 ±0.37	0.04	0.989
Deceleration time (msec)	199.86 ±57.16	197.13 ±68.48	176.25 ±46.65	179.17 ±51.67	0.69	0.564
Isovolumetric relaxation time (msec)	75.24 ±11.23	69.73 ±10.69	74.56 ±17.26	78.00 ±13.01	1.00	0.398
Left ventricular ejection fraction (%)	61.34 ±9.87	57.67 ±10.23	55.43 ±11.44	58.89 ±12.23	0.76	0.524
G2, n = 22						
E wave velocity (cm/sec)	64.66 ±21.70	69.44 ±29.28	52.26 ±14.47	61.90 ±21.89	2.29	0.084
A wave velocity (cm/sec)	76.99 ±13.06	72.12 ±11.85	74.18 ±7.84	77.13 ±26.96	0.46	0.708
E\A ratio	0.85 ±0.32	0.82 ±0.27	0.71 ±0.20	0.86 ±0.05	1.91	0.134
Deceleration time (msec)	199.43 ±40.19	171.29 ±46.05	187.00 ±37.02	180.33 ±33.20	1.74	0.166
Isovolumetric relaxation time (msec)	78.86 ±12.13	85.14 ±9.75	76.20 ±11.41	79.89 ±9.85	2.66	0.055
Left ventricular ejection fraction (%)	63.55 ±11.23	61.39 ±12.45	59.22 ±10.22	61.34 ±11.55	0.53	0.663
G3, n = 24						
E wave velocity (cm/sec)	66.02 ±15.25	71.49 ±19.99	43.65 ±27.79	76.30 ±19.09	11.31	0.000
A wave velocity (cm/sec)	60.30 ±13.12	63.48 ±13.98	69.60 ±28.85	57.60 ±7.35	2.04	0.114
E\A ratio	1.15 ±0.40	1.20 ±0.50	0.77 ±0.72	1.24 ±0.66	3.30	0.024
Deceleration time (msec)	172.00 ±42.15	201.25 ±44.98	195.50 ±51.62	187.50 ±31.82	2.07	0.110
Isovolumetric relaxation time (msec)	72.50 ±18.48	70.50 ±10.85	70.00 ±28.28	62.50 ±3.54	1.45	0.233
Left ventricular ejection fraction (%)	60.49 ±9.33	54.21 ±14.45	52.23 ±10.29	50.77 ±13.56	3.01	0.034

(IVRT) was measured, by continuous wave Doppler, as the time between the aortic closing and transmitralic flow beginning, by placing the Doppler cursor between the left ventricular outflow area and the mitral valve.

Statistical Analysis

Data were stored and analyzed by the SPSS package. One-way and 2-way analysis of variance and unpaired t test were used for parametric variables comparison between groups. Data are expressed taking the standard deviation mean as the index of dispersion. Linear regression analysis was performed to evaluate the relationship between isovolumetric relaxation time with EPI and DOX dose in all the study groups. P values less than 0.05 were considered statistically significant.

Results

Diastolic Function

After a 12-month follow-up period, the patients showed a good conservation of diastolic function in both G1 and G2 groups. No statistically significant difference was observed in E wave and A wave velocity and E/A ratio after ANT treatment. DT was decreased after treatment both in G1 ($f = 0.69$, $p = 0.564$) and in G2 ($f = 1.74$, $p < 0.166$) patients (Table III). IVRT was slightly prolonged at T3 in G1 group ($f = 1.00$, $p = 0.398$) but it was unchanged in G2 patients ($f = 2.64$, $r = 0.055$) (Table III). In G3 subjects only, E wave velocity was increased at T1 (71.49 ±19.99 cm/sec) and T3 (76.30 ±19.09 cm/sec) with statistical relevance ($f = 11.31$, $p < 0.001$). E/A ratio was evaluated at T2 less than 1 (0.77 ±0.72) in G3 group, but returned greater than 1 at T3 (Table III).

Systolic Function

Systolic dysfunction developed in only 2 subjects undergoing ANT treatment. In all 3 groups, ejection fraction decreased after cumulative DOX dose of 180 mg/m^2 by no more than 10% of T0 measurement (Figure 1). Cumulative EPI dose of 960 mg/m^2 or greater had a similar effect on the ejection fraction of all treated patients. Clinically manifest or clinical evidence of CHF did not develop after ANT treatment.

Patients with Complete Follow-up Data

Data of non-cardiac toxicity are expressed in Table IV. Common consequences of ANT chemotherapy were observed in all the study groups. A negligible amount of pericardial fluid, without hemodynamic consequences, was observed in approximately 90% of patients. A cardioprotective effect, comparable with DEX, was obtained by TMZ against ANT toxicity in the study groups. Oral administration of TMZ seems to be effective in myocardial cytoprotection as a valid alternative choice in preventing ANT cardiotoxicity.

Toxicity

A severe neutropenia was observed in approximately 54% of patients. Hyperbilirubinemia and transaminase increases were reported in 14%.

Discussion

Chronic ANT therapy is linked to impaired diastolic function as manifested by the impaired relaxation flow pattern.[12] Recent observations have

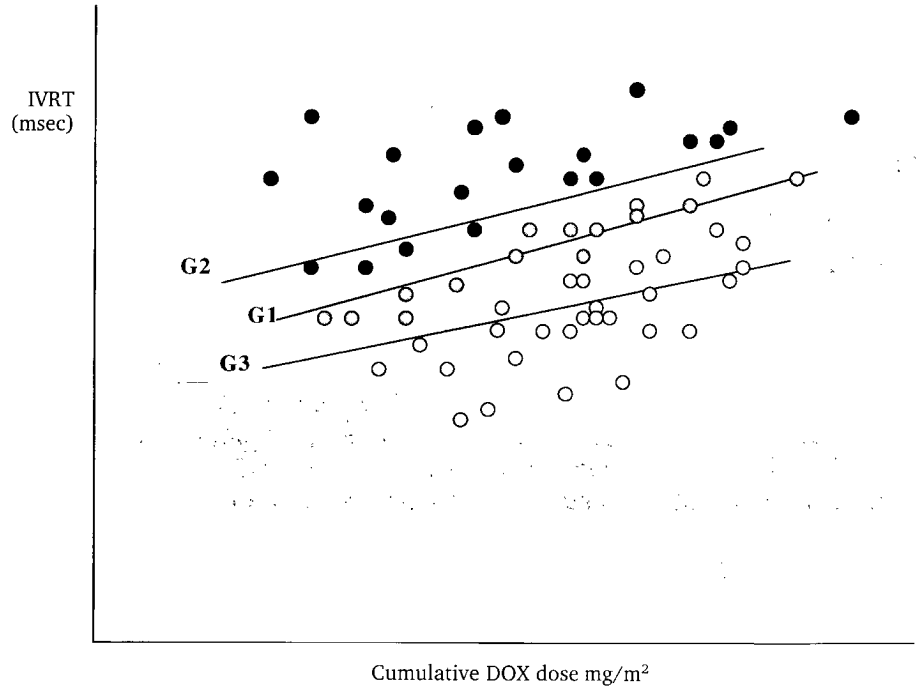

Figure 1.
Linear regression analysis of IVRT and cumulative DOX dose in G1 (A), G2 (B), and G3 (A) groups.

● G1 patients
○ G2 patients
○ G3 patients

Table IV. Noncardiac toxicity in all patients.

Effect	G1	G2	G3
Anemia	66.56%	28.57%	49.58%
Thrombocytopenia	21.34%	27.99%	51.45%
Neutropenia	61.65%	29.46%	24.77%
Hepatic toxicity	15.77%	14.34%	11.59%

suggested that diastolic filling abnormalities may predict systolic dysfunction in patients receiving DOX,[22,23] but it is uncertain whether impaired systolic function due to DOX therapy can be predicted by a noninvasive index of diastolic function, and few data exist on acute and potentially long-term effects of DOX on left ventricular filling.[24]

Cardiotoxicity Evaluation During ANT Chemotherapy: Invasive Methods

Radionuclide cardiac angiography and cardiac radioimmunoscintigraphy using Indium-111 antimyosin monoclonal antibodies have been widely used to monitor cardiotoxicity and cardiac function during ANT chemotherapy, but the sensitivity of radionuclide cardiac angiography[11] is often too low for the test to be of value as an early indicator of CHF. As for cardiac radioimmunoscintigraphy, this invasive technique is associated with risks and complications and it cannot be used in serial determinations of cardiotoxicity during ANT therapy. Endomyocardial biopsy[12] is useful in guiding ANT therapy, but it is an invasive and not repeatable procedure.

Cardiotoxicity Evaluation During ANT Chemotherapy: Noninvasive Methods

Electrocardiography and M-mode echocardiography are insensitive and nonspecific in monitoring ANT-induced cardiotoxicity, so it is unclear which noninvasive study is most useful in the early detection of ANT cardiotoxicity or in guiding the maximally tolerable dose in patients with malignant neoplasms. The fractional shortening of the minor diameter of the left ventricle and the velocity of circumferential fiber shortening have been used, but these measures are largely dependent on synchronous ventricular wall motion and loading conditions. Ejection fraction has been used in the detection of DOX cardiotoxicity but it correlates poorly with myocardial biopsy grades of DOX cardiac damage, and it seems insensitive, at rest, to predict mild congestive heart failure.[25] On the contrary, pulsed Doppler indices of diastolic filling can unveil preclinical cardiac dysfunction in patients at risk of development of ANT-induced systolic failure. Isovolumetric relaxation time was 78% sensitive and 88% specific in detecting DOX-induced changes in ejection fraction.[26]

DOX administration was found to prolong both IVRT and DT and to decrease peak early to atrial filling velocity ratio and deceleration rate of early filling, with persistent effects on diastolic filling and systolic function for more than 3 months after treatment.[26]

Conclusions

Effect on Diastolic Function

Filling indices of diastolic function may be more sensitive than variables of systolic function in predicting ANT induced congestive heart failure. Shortly after administration, ANT prolongs isovolumetric relaxation time, with adverse effects on this variable persisting at least three months after cessation of treatment.[26] In all the patients of this study, myocardial cytoprotection minimized the negative myocardial consequences of anthracycline toxicity on diastolic function pre-

serving filling performance also after 1 year of follow-up (Table III).

Subacute and Chronic Effects of DOX and EPI Therapy

The risk of delayed cardiotoxicity[27] was monitored in all the patients. No clinical or echocardiographic evidence of toxic myocarditis or pericarditis were found as subacute effects of chemotherapeutic drugs in all the study groups. Cardiomyopathy and subsequent congestive heart failure were not observed in any patient.

Myocardial Cytoprotection by TMZ and DEX

TMZ and DEX attained comparable cytoprotective effect in G1, G2, and G3 through long-term follow-up after ANT treatment. The ability of DEX to provide myocardial cytoprotection has been validated in current literature.[28] In G3 patients, E/A ratio was essentially unchanged at T2, and DT and IVRT showed no statistically significant variation at T1 and T2 times. The antiischemic effect of TMZ[29-32] has been tested both in clinical and laboratory settings[33,34] and ANT cardiotoxic effects toward cytopathogenetic damage are demonstrated late after treatment in young hearts.[35,36] Echocardiographic monitoring is actually needed for detecting subclinical toxicity[37] during ANT treatment to avoid negative consequences on left ventricular diastolic function and systolic performance. Oral administration of a cytoprotective drug could be better tolerated by patients undergoing cytotoxic anticancer chemotherapy.

Limitations of the Study

In the absence of the development of CHF, no standard definition of DOX or EPI cardiotoxicity exists. From the primitive observation of cardiac toxicity after adriamycin administration,[38] several clinical and pathologic observations about ANT chemotherapy were executed. However, the echocardiographic monitoring of ANT toxicity was prospective, reasonably repeatable and parallel with clinical guidelines in the use of ANT in the antineoplastic drug treatment. Interobserver and intraobserver variability of the 2-dimensional echocardiographic measurements are the obvious limitations of the study, but the reliability of the calculation of left ventricular ejection fraction by 2-dimensional echocardiography[39] and of Doppler echocardiographic indexes have been demonstrated by previous observations.[26]

REFERENCES

1. Singh B: Mechanism of action of a novel metabolically active antianginal agent (trimetazidine) delineated by PET. J Am Coll Cardiol 27:132A, 1996.
2. Maridonneau Parini I, Harpey C: Effects of trimetazidine on membrane damage reduced by oxygen free radicals in human red cells. Br J Clin Pharmacol 20:148-151, 1985.
3. Detry JM, Sellier P, Pennaforte S, et al, on behalf of the Trimetazidine European Multicenter Study Group: Trimetazidine: A new concept in the treatment of angina. Comparison with propranolol in patients with stable angina. Br J Clin Pharmacol 37: 279-288, 1994.
4. Detry JM, Leclerq BS: Trimetazidine European multicenter study vs. propranolol in stable angina pectoris; contribution of Holter electrocardiographic ambulatory monitoring. Am J Cardiol 76:8B-11B, 1995.
5. Michaelides AP, Vyssoulis GP, Bonoris PE, et al: Beneficial effects of trimetazidine in men with stable angina under beta blocker treatment. Curr Ther Res 46:565-576, 1989.
6. Steg PG, Grollier G, Galley P, et al: A randomized double-blind trial of trimetazidine as adjunctive therapy to primary PTCA for acute myocardial infarction: evidence for improved myocardial reperfusion from ST-segment analysis. Eur Heart J 19:2046, 1998.
7. Kober G, Buck T, Sievert H, et al: Myocardial protection during percutaneous transluminal coronary angioplasty: Effects of trimetazidine. Eur Heart J 13:1109-1115, 1992.
8. Belardinelli M, Purcaro A: Trimetazidine improves the contractile response of hibernating myocardium to low-dose dobutamine in ischemic cardiomyopathy. Circulation 98:3727, 1998.
9. Lu C, Dabrowski P, Fragasso G, et al: Effects of trimetazidine on ischemic left ventricular dysfunction in patients with coronary artery disease. Am J Cardiol 82:898-901, 1998.
10. Bristow MR, Billingham ME, Mason JW, et al: Clinical spectrum of anthracycline antibiotic cardiotoxicity. Cancer Treat Rep 62:873-879, 1978.
11. Schwartz R, Mc Kenzie W, Alexander J, et al: Congestive heart failure and left ventricular dysfunction complicating Doxorubicin therapy: A seven year experience using serial radionuclide angiocardiography. Am J Med 82:1109-1118, 1987.
12. Mortensen SA, Olsen HS, Baandrup U: Chronic anthracycline cardiotoxicity; hemodynamic and histopathological manifestations suggestive a restrictive endomyocardial disease. Br Heart J 55:274-282, 1986.

13. Praga C, Beretta G, Vigo PL: Adriamycin cardiotoxicity: A survey of 1273 patients. Cancer Treat Rep 63:827-834, 1979.

14. Von Hoff DD, Layard MW, Basa P: Risk factors for doxorubicin induced congestive heart failure. Ann Intern Med 91:710-717, 1979.

15. Speyer JL, Green MD, Zeleniuch Jacquotte A: ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. J Clin Oncol 10:117-127, 1982.

16. Venturini M, Michelotti A, Del Mastro L: Multicenter randomized controlled clinical trial to evaluate cardioprotection of dexrazoxane versus no cardioprotection in women receiving epirubicin chemotherapy for advanced breast cancer. J Clin Oncol 14:3112: 3120, 1996.

17. Lopez M, Vici P: European trials with dexrazoxane in amelioration of doxorubicin and epirubicin-induced cardiotoxicity. Semin Oncol 25(4 suppl):10:55-60, 1998.

18. Nishimura RA, Tajik AJ: Quantitative hemodynamics by Doppler echocardiography: A noninvasive alternative to cardiac catheterization. Progr Cardiovasc Dis 36:309-342, 1994.

19. Vasan RS, Benjamin EJ, Levy D: Prevalence, clinical features and prognosis of diastolic heart failure: An epidemiologic perspective. J Am Coll Cardiol 26: 1565-1574, 1995.

20. European Study Group on Diastolic Heart Failure: How to diagnose diastolic heart failure. Eur Heart J 19:990-1003, 1998.

21. Takatsuji H, Mikami J, Urasawa K, et al: A new approach for evaluation of left ventricular diastolic function: Spatial and temporal analysis of left ventricular filling flow propagation by color M-mode Doppler echocardiography. J Am Coll Cardiol 27:365-371, 1996.

22. Lee BH, Goodenday LS, Muswick GJ, et al: Alterations in left ventricular diastolic function with doxorubicin therapy. J Am Coll Cardiol 9:184-188, 1987.

23. Marchandise B, Scroeder E, Bosly, et al: Early detection of doxorubicin cardiotoxicity: Interest of Doppler echocardiographic analysis of left ventricular filling dynamics. Am Heart J 118:92-98, 1989.

24. Brown KA, Blow AJ, Weiss RM, et al: Acute effects of doxorubicin on human left ventricular systolic and diastolic function. Am Heart J 118:92-98, 1989.

25. Alexander J, Dainiak N, Berger HJ, et al: Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med 300:278-283, 1979.

26. Stoddard HF, Seeger J, Liddel NE, et al: Prolongation of isovolumetric relaxation time as assessed by Doppler echocardiography predicts doxorubicin-induced systolic dysfunction in humans. J Am Coll Cardiol 20:62-69, 1992.

27. Allen A: The cardiotoxicity of chemotherapeutic drugs. Semin Oncol 19:529-542, 1992.

28. Lopez M, Vici P, Di Lauro L, et al: Randomized prospective clinical trial of high dose epirubicin and dexrazoxane in patients with advanced breast cancer and soft tissue sarcoma. J Clin Oncol 16:89-92, 1998.

29. Levy S, Group of South France Investigators. Combination therapy of trimetazidine with diltiazem in patients with coronary artery disease. Am J Cardiol 76:6B-12B, 1995.

30. Fantini E, Demaison L, Sentax E, et al: Some biochemical aspects of the protective effect of trimetazidine on rat cardiomyocites during hypoxia and reoxygenation. J Mol Cell Cardiol 26:949-958, 1994.

31. Allibardi S, Chierchia SL, Cerioli V, et al: Trimetazidine reduces post-ischemic dysfunction in rat hearts by decreasing energy requirements during underperfusion. J Cardiovasc Pharmacol 22:640-647, 1998.

32. Detry MJ: TEMS: Double-blind comparison of trimetazidine and propranolol in stable angina pectoris. J Am Coll Cardiol 31:36-47, 1998.

33. Morin D, Sapena R, Elimadi A, et al: [(3)H]–trimetazidine mithocondrial binding sites: Regulation by cations, effect of trimetazidine derivatives and other agents and interaction with an endogenous substance. Br J Pharmacol 130:655-663, 2000.

34. Kantor PF, Lucien A, Kozak R, et al: The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mithocondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res 17;86(5):580-585, 2000.

35. Leandro J, Dyck J, Poppe D, et al: Cardiac dysfunction late after cardiotoxic therapy for childhood cancer. Am J Cardiol 74:1152-1156, 1994.

36. Bu'Lock FA, Mott MG, Oakhill A, et al: Left ventricular diastolic function after anthracycline chemotherapy in childhood: Relation with systolic function, symptoms and pathophysiology. Br Heart J 73:340-350, 1995.

37. Cittadini A, Fazio S, D'Ascia C, et al: Subclinical cardiotoxicity by doxorubicin: A pulsed Doppler echocardiographic study. Eur Heart J 12:1000-1005, 1999.

38. Lefrak EA, Pitha J, Rosenheim S: A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 32:302-314, 1973.

39. Wyatt HL, Haendchen RV, Meerbaum S, et al: Assessment of quantitative methods for 2-dimensional echocardiography. Am J Cardiol 5:396-401, 1983.