EFFECTS OF LONG-TERM XAMOTEROL IN IDIOPATHIC DILATED CARDIOMYOPATHY

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In prospective study, the β_1-partial agonist xamoterol (200 mg daily) was given to 26 patients with idiopathic dilated cardiomyopathy (DCM) in addition to conventional therapy with digitalis, diuretics and vasodilators. The patients were followed for 35 ± 15 months (6-53 months). Cardiothoracic ratio (CTR), left ventricular end-diastolic dimension (LVDD) and exercise heart rate decreased, and exercise duration, fractional shortening (FS) and ejection fraction (EF) increased after xamoterol therapy. Twenty-one patients survived and one patient dropped out at 7 months. Twelve of the 20 patients improved their NYHA functional class. Blood norepinephrine concentration (NE), LVDD, FS, EF and pulmonary capillary wedge pressure (PCWP) after xamoterol were significantly better in survivors than in non-survivors. Survival rate at 3 years was 83%.

The results suggest that adjunctive xamoterol therapy in DCM has a beneficial effect on hemodynamics and symptoms. Prognosis will be satisfactory if improvement in parameters such as NE, LVDD, FS, EF and PCWP is seen during xamoterol therapy. (*Jpn Circ J* 1992; **56:** 12–20)

IDIOPATHIC dilated cardiomyopathy (DCM) is a disease of unknown etiology which is characterized by left ventricular dilatation and reduced contractility. The prognosis is variable, but is generally poor[1,2] At present, DCM is treated mainly by potentiation of cardiac contractile force with cardiotonics and by lowering of the load with diuretics or vasodilators, however, the therapeutic effects of those treatments are not always satisfactory[3]

In patients with DCM, depressed cardiac function increases the catecholamine levels in the blood, which adversely affect the myocardium and further lower cardiac contractile force[4]

Waagstein et al have reported that β-blockers are useful for selected DCM patients with heart failure and several further studies confirm their results[5]

Xamoterol (ICI 118, 587, Corwin) is a partial agonist which acts on β_1-receptors, with 43% of the maximum acivity of isoprenaline[6] When sympathetic tone is relatively high, xamoterol acts as an antagonist. Because of its pharmacological properties xamoterol stabilizes the response of the heart to sympathetic stimulation. Thus, it is considered that xamoterol is useful in DCM, because it may improve the cardiac function through its mild potentiating action on cardiac contraction, and because it may protect

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TABLE I BASELINE CHARACTERISTICS OF PATIENTS (N=26)

Sex	*females*	*6*
	males	*20*
Age (years)		*26-71 (53±12)*
Duration of follow up (months)		*6–53 (35±15)*
NYHA class		
	I	*0*
	II	*10*
	III	*15*
	IV	*1*
Cardiothoracic ratio (%)		*42–72 (58±8)*
LVDD (cm)		*5.1–8..5 (6.2±0.9)*
Fractional shortening (%)		*5–28 (14±7)*
Ejection fraction (%)		*10±48 (26±11)*
Medications (n)		
	Digoxin	*24*
	Diuretics	*22*
	Vasodilators	*16*
	Antiarrhythmics	*9*
	Anticoagulants	*15*

Values are mean±1 standard deviation
LVDD=left ventricular end-diastolic dimension
NYHA=New York Heart Association

the heart from the cardiotoxic effects of excessive catecholamines[6,7]

In the present study, long-term effects of xamoterol on patients with DCM were examined.

MATERIALS AND METHODS

Between 1985 and 1987, 86 patients were diagnosed as DCM after cardiac catheterization, endomyocardial biopsy or echocardiography, according to the diagnosis criteria of WHO/ISFC. They were followed up at Niigata University, Kuwana Hospital and Sannocho Hospital[8,9] At random, 26 patients were enrolled in the study. They were composed of 20 males and 6 females, and their age was 26–71 years (mean±1 SD; 53±12 years). Ten, 15 and 1 patients were diagnosed as New York Heart Association (NYHA) functional class II, III and IV respectively. While 17 patients were in sinus rhythm, the other 9 had atrial fibrillation.

The coronary arteries of all the patients were normal. Secondary cardiomyopathy such as myocarditis was excluded by endomyocardial biopsy. The patients had been treated with conventional therapy for cardiac failure or arrhythmias, such as digitalis, diuretics, vasodilators and antiarrhythmics (Table I). The duration of illness was 2 months to 5 years (14±16 months).

After it was ascertained (by monitoring for 1 month) that the subjective symptoms of the patients were stable, patients were started in the study. Prior to the study, verbal informed consent in the study was obtained from all patients.

The short-term effects of xamoterol were observed by administering 0.2 mg/kg intravenously to 13 patients through a Swan-Ganz catheter[9]

Xamoterol 100 mg was administered twice daily (200 mg/day). Previous therapy such as digitalis, diuretics, vasodilators and anticoagulants were continued during the study, without their dosage and administration being modified, if possible. Patients who had been treated with β-stimulants or β-blockers were excluded. One patient who had NYHA class IV, received 50 mg of xamoterol b.i.d. (100 mg per day) for first 7 days, and 100 mg b.i.d. from 8th day. Treatment with xamoterol continued for 6–53 months (35±15 months).

Norepinephrine concentration in the blood and the β-receptor density in lymphocytes were determined in 8 patients. As reported previously, the norepinephrine concentration was determined by high performance liquid chromatography, and the density of β-receptors in lymphocytes isolated from 10 ml blood was measured by radioligand binding assay with ^{125}I-iodocyanopindolol[9]

Left ventricular end-diastolic dimension (LVDD) and left ventricular end-systolic dimension were determined by echocardiography, and left ventricular fractional shortening (FS) and left ventricular ejection fraction (EF) were calculated.

Exercise tolerance was determined in 26 patients (the tolerance time of NYHA class IV patients was determined as 0 min) by an exercise test with a supine bicycle ergometer. The load was started with 25 watts and gradually increased by 25 watts at 3 min intervals (multistage loading method), and the test was discontinued when such subjective symptoms such as dyspnea, fatigue, hypotension, chest pain or severe arrhythmias developed.

Hemodynamic parameters such as pul-

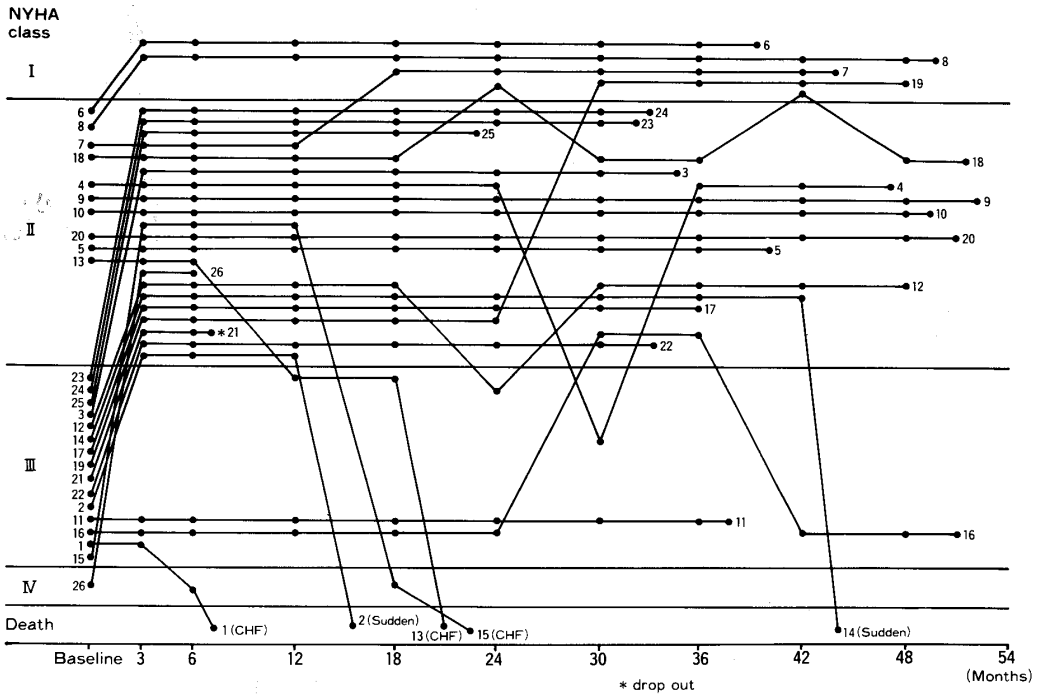

Fig.1. Flow chart of New York Heart Association functional classification and mortality during long-term treatment of xamoterol (200 mg/day).
CHF=congestive heart failure

monary capillary wedge pressure (PCWP) and cardiac index (CI) were measured by a Swan-Ganz catheter.

Subjective symptoms, NYHA functional classes, physical parameters and hemodynamic parameters were recorded at 6—18 month intervals.

The cumulative survival curve was drawn by the Kaplan-Meier method. When the p value was less than 0.05, the difference was regarded as statistically significant. All data obtained were expressed in the mean±1 SD.

RESULTS

Survival curve and clinical course (Fig. 1 and 3).

The 3 year survival rate of the basal treatment plus xamoterol was 83%.

Three patients died of heart failure after they were treated with xamoterol for 7 (no.1), 21 (no.13) and 22 months (no.15) respectively. One (no.1) out of the 3 patients had NYHA class III before xamoterol therapy, her NYHA class became II for 2 months and then returned to III during xamoterol therapy, ending in death due to left cardiac failure. The second patient (no.13) had NYHA class II before xamoterol therapy. His NYHA class became III and left cardiac failure was not improved during xamoterol thrapy. Xamoterol was stopped at 19 months and he died at 21 months. The third patient (no.15) had NYHA class III before xamoterol therapy, which improved to II; the NYHA class hardly changed during one year of xamoterol therapy but the patient died of worsened cardiac failure after 22 months of xamoterol therapy.

Two patients died suddenly after they were treated with xamoterol for 15 (no.2) and 45 months (no.14) respectively. One patient (no.2) had NYHA class III accompanied by ventricular tachycardia before xamoterol therapy and NYHA class was improved to II for 12 months by xamoterol therapy. The patient was treated with xamoterol and procainamide, and died suddenly after 15 months of the combined therapy. The other patient (no.14) had NYHA class III and sinus rhythm along with sporadic ventricular premature beats before xamoterol therapy. Although NYHA class was improved to II and ventricular tachycardia was not found in 24h Holter electorcardiogram during xamoterol therapy, the patient died suddenly after 45 months of xamoterol therapy.

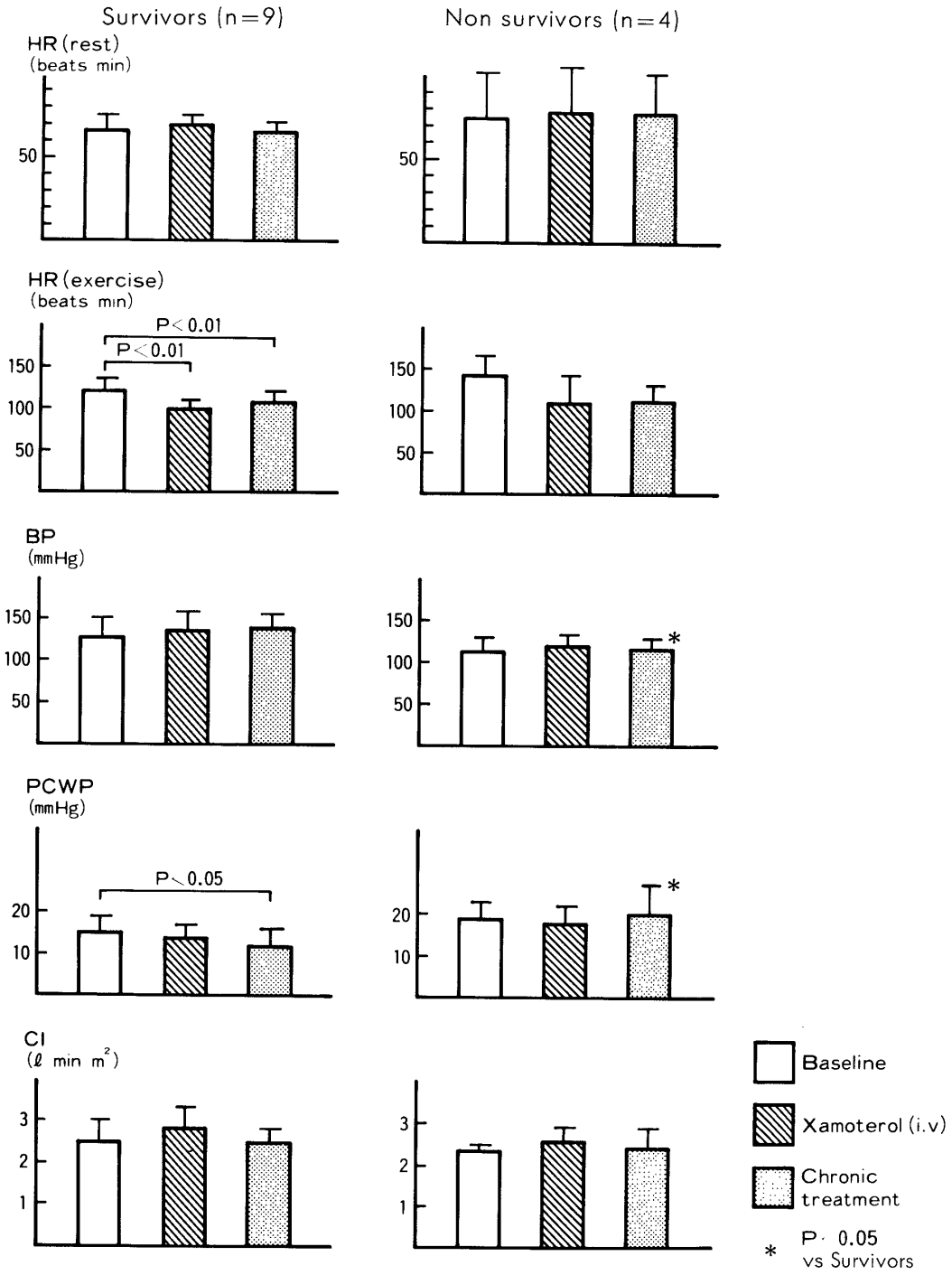

Fig.2. Short-term intravenous xamoterol administration (0.2 mg/kg) in survivors (n=9) and non-survivors (n=4).
BP=blood pressure; CI=cardiac index; HR=heart rate; PCWP=pulmonary capillary wedge pressure

Long-term effect of xamoterol in all 26 patients (Table II).

Worsening of heart failure, new development of arrhythmias and hypotension were not observed in any patient during the first 3 months of xamoterol therapy, which enabled xamoterol therapy to be continued for 6 months or longer. Twenty-one of 26 patients survived and one patient dropped out at 7 months. Thirteen out of the 20 survivors improved their NYHA class from 2.8 ± 0.5 to 1.7 ± 0.5 ($p<0.001$) (Fig. 1).

Twenty-four hours Holter electrocardiographic monitoring demonstrated ventricular

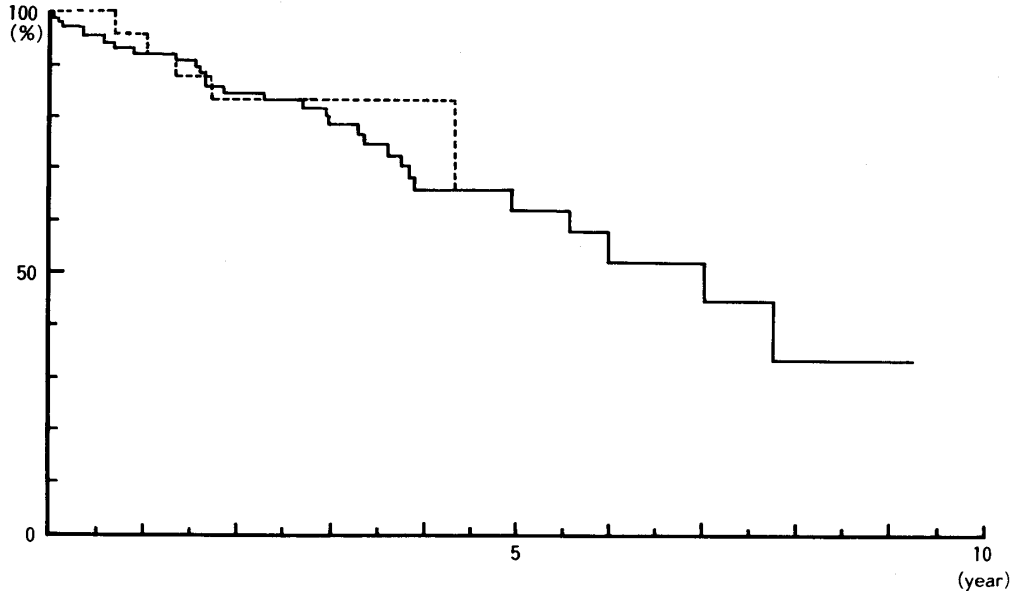

Fig.3. Comulative durvival rate curves (Kaplan-Meier) of patients with idiopathic dilated cardiomyopathy. Patients were treated with conventional therapy (non-xamoterol, solid line, n=110) or with xamoterol adjunctive to conventional therapy (dotted line, n=26).

TABLE II LONG-TERM EFFECT OF XAMOTEROL IN ALL PATIENTS

	Baseline	*Long-term*
Ventricular tachycardia (n)	*9*	*6*
Cardiothoracic ratio (%)	*58±8*	*54±7**
Exercise tolerance (min)	*5.6±2.3*	*7.2±2.2**
Left ventricular end-diastolic dimension (cm)	*6.2±0.9*	*5.8±1.0**
Fractional shortening (%)	*14±7*	*21±10**
Ejection fraction (%)	*26±11*	*37±15**
Exercise heart rate (beats/min)	*126±18*	*112±16**
Resting heart rate (beats/min)	*78±18*	*74±14*
Systolic blood pressure (mmHg)	*119±17*	*127±17*
Norepinephrine (ng/ml)	*0.52±0.27*	*0.49±0.28*
β-receptors (sites/cell)	*1024±413*	*1584±650*
Cardiac index (l/min/m²)	*2.41±0.39*	*2.48±0.37*
Pulmonary capillary wedge pressure (mmHg)	*16±5*	*14±6*

*$p<0.05$, **$p<0.01$ vs baseline*

premature contractions in all 26 patients and ventricular tachycardia in 9 patients before xamoterol therapy. Ventricular tachycardia disappeared in 3 of the 9 patients after xamoterol therapy, and new development of ventricular tachycardia was not observed in any other patient.

Cardiothoracic ratio was reduced significantly from 58±8% before xamoterol therapy to 54±7% after xamoterol ($p<0.05$). Mean exercise duration increased from 5.6±2.3 to 7.2±2.2 min ($p<0.05$). LVDD in echocardiography decreased from 6.2±0.9 cm to 5.8±1.0 cm ($p<0.05$). FS increased from 14±7% to 21±10% ($p<0.05$). EF increased from 26±11% to 37±15% ($p<0.05$). Exercise heart rate decreased significantly from 126±18 to 112±16 beats per min ($p<0.01$).

Resting heart rate, systolic blood pressure, norepinephrine, density of β-receptors in lymphocytes, CI and PCWP did not change after xamoterol therapy.

TABLE III COMPARISON BETWEEN BASELINE AND LONG-TERM TREATMENT CLINICAL AND HEMODYNAMIC VARIABLES IN SURVIVORS (N=20) AND NON-SURVIVORS (N=5).

	Baseline		*long-term trearment*	
	survivors	*non-survivors*	*survivors*	*non-survivors*
Years	*52±12*	*57±10*		
NYHA (no.)				
I	*0*	*0*	*4*	*0*
II	*9*	*1*	*14*	*2*
III	*10*	*4*	*2*	*1*
IV	*1*	*0*	*0*	*2*
Cardiothoracic ratio (%)	*56±7*	*64±8*	*53±6**	*60±7*
Exercise tolerance (min)	*5.8±2.4*	*5.2±2.0*	*7.7±2.2***	*5.6±1.5*
Resting heart rate (beats/min)	*67±9*	*75±27*	*66±6*	*77±23*
Exercise heart rate (beats/min)	*122±15*	*143±21*	*108±15***	*112±19*
Resting systolic blood pressure (mmHg)	*129±21*	*114±16*	*139±17*	*116±13#*
Atrial fibrillation (n)	*8*	*1*	*9*	*1*
Ventricular tachycardia (n)	*7*	*2*	*4*	*2*
Left ventricular end-diastolic dimension (cm)	*6.1±0.8*	*6.9±1.0*	*5.6±0.8***	*6.7±0.9#*
Fractional shortening (%)	*14±7*	*14±3*	*23±10***	*12±3#*
Ejectional fraction (%)	*26±12*	*27±6*	*40±15**	*23±4#*
Norepinephrine (ng/ml)	*0.41±0.21*	*0.65±0.36*	*0.37±0.14*	*0.85±0.25#*
β-receptors (sites/cell)	*1130±484*	*847±119*	*1849±645*	*1142±348*
Cardiac index (l/min/m²)	*2.51±0.50*	*2.34±0.16*	*2.50±0.33*	*2.42±0.49*
Pulmonary capillary wedge pressure (mmHg)	*15±4*	*19±4*	*12±4**	*20±7#*

*$p<0.05$ **$p<0.01$ VS baseline and #$p<0.05$ VS survivors

Comparison between survivors and non-survivors.

The parameters before xamoterol therapy (Table III).

The age, exercise tolerance time, heart rate, blood pressure, LVDD, FS, EF, CI and PCWP at the start of xamoterol therapy were not significantly different between survivors and non-survivors.

Short-term intravenous xamoterol therapy (Fig. 2).

Short-term effects of xamoterol administered intravenously at 0.2 mg/kg to 13 patients were compared with its long-term effects. Exercise heart rate was decreased in both survivors (from 122±15 to 100±10 beats/min, $p<0.01$) and non-survivors (from 143±21 to 110±33 beat/min, $0.05<p<0.1$) after xamoterol therapy, but heart rate at rest, systolic blood pressure, PCWP and CI were unchanged. None of the above parameters were significantly different between survivors and non-survivors.

Long-term therapy (Table III and Fig. 2).

Cardiothoracic ratio, exercise tolerance, LVDD (from 6.1±0.8 to 5.6±0.8 cm, $p<0.01$), FS, EF and PCWP were improved after xamoterol therapy in survivors, while those of non-survivors were unchanged. Exercise heart rate was decreased after xamoterol therapy in both survivors and non-survivers. However, it was not significantly different between the two groups.

Systolic blood pressure, LVDD, FS, EF, norepinephrine and PCWP were significantly different between survivors and non-survivors.

Norepinephrine concentration in blood.

The norepinephrine concentration before xamoterol therapy was 0.41±0.21 and 0.65±0.36 ng/ml in survivors and non-survivors respectively, indicating higher levels in both of them than in healthy subjects (0.23±0.08 ng/ml);[10] however, no significant difference was noted between survivors and non-survivors. After xamoterol therapy, the norepinephrine concentration of survivors was reduced to 0.37±0.14 ng/ml, whereas that of non-survivors was maintained at a high level (0.85±0.25 ng/ml). As a result,

the norepinephrine after xamoterol therapy was significantly higher in non-survivors than in survivors ($p<0.05$).

β-receptor binding study.

The density of β-adrenergic receptors in lymphocytes before xamoterol therapy was lower in survivors and non-survivors than in healthy subjects (1466 ± 373 sites/cell)[9] The density in survivors was increased into normal zone during xamoterol therapy from 1130 ± 484 to 1849 ± 645 sites/cell, whereas that of non-survivors during xamoterol therapy was lower than that of healthy subjects.

DISCUSSION

Long-term prognosis of DCM is extremely poor. Fuster et al[11] have reported that the 5 year survival rate of DCM patients is 38%. Otsuka had reported[12] that 3 year and 5 year survival rates are 78 and 68% respectively in 110 patients with DCM and that the 3 year survival rate of patients with sustained ventricular tachycardia is very low (32%).

The etiology of DCM has not been clarified so far. Therefore, only symptomatic therapy has been given to DCM patients. Digitalis, diuretics, vasodilators and oral cardiotonics have been prescribed for heart failure.

Antiarrhythmics have also been prescribed for a variety of arrhythmias, however, the risk of sudden death has not been mitigated. Although new therapies with implantable defibrillators or electrical ablation have been introduced, their therapeutic value has not been established[11,13] On the other hand, heart transplantation has been applied to the treatment of DCM patients with satisfactory therapeutic results, but it is applicable only to a limited number of patients in a limited number of institutions at present.

Oral cardiotonics have been developed recently, and their clinical usefulness for treatment of chronic cardiac failure has been examined[14,15] Although short-term effects on hemodynamics are widely accepted, the usefulness of long-term therapy or their influence on the prognosis of DCM has not been definitely established. Rather, they may possibly worsen the prognosis of DCM patients by promoting exhaustion of the myocardium with already lowered contractility or by inducing a fatal arrhythmia.

Intriguingly, it has been reported that β-blockers are useful for DCM patients[16,17] It is argued that β-blockers are effective at least on a certain type of DCM patients, because they may improve diastolic performance of the myocardium and protect the myocardium from excessive catecholamines[18] Generally, however, β-blockers are considered to worsen cardiac failure through depression of cardiac function, and so they have been prescribed to DCM patients in only a limited number of institutions. As cardiac failure can be worsened in the early stage of β-blocker therapy, it is necessary to start with a low dose and increase dosage carefully while monitoring the symptoms of patients.

Xamoterol, a β_1-partial agonist, is approximately 0.43 times as potent as isoprenaline in agonist activity. Therefore, xamoterol may improve or maintain the cardiac function of a failing heart through its mild myocardial stimulating activity while its β-blocking effect protects the myocardium from excessive catecholamines. Pouleur et al have shown that xamoterol administration improved relaxation and lowered mean diastolic wall stress in heart failure patients[19] Another study has shown that left ventricular filling pressure remains lower during exercise with xamoterol[20] The effects of xamoterol on diastolic function might therefore be an important mechanism underlying the improved exercise tolerance observed in heart failure patients.

In the present study, we examined the short-term effects of intravenous xamoterol in 13 patients with DCM. No significant changes were observed at rest in either survivors or non-survivors. This result may be explained by the partial agonist activity of xamoterol, because the blood norepinephrine concentration of the present patients was 0.5 ± 0.27 ng/ml at rest[9] HR at exercise was significantly decreased after intravenous xamoterol therapy. PCWP, CI, BP and HR at rest were unchanged after intravenous xamoterol injection even in patients with high blood norepinephrine concentrations (not less than 0.70 ng/ml) at rest. This indicates that the β-blocking activity of xamoterol at rest is only mild. Therefore, it is reasoned that the combined mild stimulatory and protective effects of xamoterol on

the myocardium enable its safe application to DCM patients. Thus, we started long-term xamoterol therapy in DCM patients.

The long-term effects of oral xamoterol 200 mg/day were examined in 26 patients with DCM. Subjective symptoms and NYHA class were improved in 20 patients after 1–3 months of xamoterol therapy, and the therapeutic effects of xamoterol were maintained or augmented in most patients during long-term xamoterol therapy. It can be said that long-term xamoterol therapy improved the quality of life of DCM patients, without producing tachyphylaxis. A variety of parameters measured before xamoterol therapy were not significantly different between survivors and non-survivors. In contrast, after xamoterol therapy, the blood norepinephrine concentration, LVDD and PCWP were reduced while the density of β-receptors in lymphocytes, FS and EF were increased in survivors compared with non-survivors.

The survival rate was compared by the generalized Wilcoxon test between the present study and a previous study with 110 patients with DCM[12] The 3-year suvival rates for the basal treatment group and basal treatment plus xamoterol group was 78% and 83% respectively, with no significant difference between the 2 groups (Fig. 3). It has been reported that 3-month survival probabilities for the xamoterol group and the placebo group were 91% and 96%, in patients with severe heart failure (NYHA III and IV) treated with xamoterol 200 mg twice daily[21] In our study, patients were treated with xamoterol 100 mg twice daily; one patient who had NYHA IV received 50 mg twice daily for the first 7 days, followed by 200 mg/day thereafter. It is important that small doses of xamoterol must be administered to heart failure patients, in a similar fashion to β-blockers[17]

Although it is difficult to predict the therapeutic effects of xamoterol prior to the start of treatment, it is expected that xamoterol will be effective and prognosis will be satisfactory if improvement in such parameters as LVDD, FS, EF, blood norepinephrine concentration and PCWP are seen during xamoterol therapy. These preliminary findings in this small study need to be confirmed in large prospective placebo-controlled studies.

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