








ORIGINAL RESEARCH

Impact of Medical Castration on Malignant Arrhythmias in Patients With Prostate Cancer

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BACKGROUND: Medical castration, gonadotropin-releasing hormone agonists, and antiandrogens have been widely applied as a treatment for prostate cancer. Sex steroid hormones influence cardiac ion channels. However, few studies have examined the proarrhythmic properties of medical castration.

METHODS AND RESULTS: This study included 149 patients who underwent medical castration using gonadotropin-releasing hormones with/without antiandrogen for prostate cancer. The changes in the ECG findings during the therapy and associations of the electrocardiographic findings with malignant arrhythmias were studied. The QT and corrected QT (QTc) intervals prolonged during the therapy compared with baseline (QT, 394 ± 32 to 406 ± 39 ms [$P<0.001$]; QTc, 416 ± 27 to 439 ± 31 ms [$P<0.001$]). The QTc interval was prolonged in 119 (79.9%) patients during the therapy compared with baseline. In 2 (1.3%) patients who had no structural heart disease, torsade de pointes (TdP) and ventricular fibrillation (VF) occurred ≥ 6 months after starting the therapy. In patients with TdP/VF, the increase in the QTc interval from the pretreatment value was >80 ms. However, in patients without TdP/VF, the prevalence of an increase in the QTc interval from the pretreatment value of >50 ms was 11%, and an increase in the QTc interval from the pretreatment value >80 ms was found in only 4 (3%) patients.

CONCLUSIONS: Medical castration prolongs the QT/QTc intervals in most patients with prostate cancer, and it could cause TdP/VFs even in patients with no risk of QT prolongation before the therapy. An increase in the QTc interval from the pretreatment value >50 ms might become a predictor of TdP/VF. Much attention should be paid to the QTc interval throughout all periods of medical castration to prevent malignant arrhythmias.

Key Words: medical castration ■ prostate cancer ■ QT prolongation ■ torsade de pointes ■ ventricular fibrillation

See Editorial by Vink and Postema

Progress in the treatment has led to an improved survival in patients with cancer, and the importance of cardiovascular disease attributable to cardiotoxicities of drugs and radiation therapy has begun to be recognized.¹ Prostate cancer is the most common noncutaneous malignancy in men, and has been steadily rising in an aging society.² Medical castration, suppressing testosterone with gonadotropin-releasing

hormone analogues, is broadly effective at any stage of localized cancer (stage A and B), locally advanced cancer (stage C), and metastatic cancer (stage D). It has been shown to be as effective as surgical castration, and, nowadays, medical castration is a cornerstone in the treatment of prostate cancer.³

Sex steroid hormones, including testosterone, influence the cardiac ion channels, and medical castration

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For Sources of Funding and Disclosures, see page 9.

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CLINICAL PERSPECTIVE

What Is New?

- Medical castration prolonged the QT and corrected QT intervals in most patients with prostate cancer and could rarely cause torsade de pointes and ventricular fibrillation.
- An increase in the corrected QT interval of >50 ms might become a predictor of malignant arrhythmias during medical castration in patients with prostate cancer.

What Are the Clinical Implications?

- Much attention should be paid to the corrected QT interval throughout all periods of medical castration to prevent torsade de pointes, ventricular fibrillation, and sudden death in patients with prostate cancer.

Nonstandard Abbreviations and Acronyms

QTc	corrected QT
ΔQTc	increase in the QTc interval from the pretreatment value
TdP	torsade de pointes

could affect the QT intervals.⁴ In fact, previously castrated men could exhibit a longer duration of the corrected QT (QTc) interval than noncastrated men.⁵ In patients with prostate cancer, medical castration is associated with QT prolongation,⁶ and could cause torsade de pointes (TdP).⁷ Recently, we also experienced a case of prostate cancer that presented TdP and ventricular fibrillation (VF) during medical castration in our hospital.⁸ A previous study reported that, in patients with hypogonadism who presented with QT prolongation and/or TdP, testosterone treatment shortened the prolonged QT intervals and prevented recurrences of TdP.⁷ However, from the therapeutic aspect of prostate cancer, a supplemental administration of testosterone should not be easily given to those patients. Few studies have systematically examined the incidence, characteristics, and risk factors of the QT prolongation, TdP, or VF in patients receiving medical castration for prostate cancer thus far. Accordingly, this study aimed to clarify these points.

METHODS

Study Patients

The data that support the findings of this study are available from the corresponding author on reasonable request. This retrospective observational study

included consecutive patients with prostate cancer who underwent medical castration using gonadotropin-releasing hormone analogues (leuproreline, 11.25 mg per 3 months; or gosereline, 3.6 mg per a month) or gonadotropin-releasing hormone antagonists (degarelix, 80 mg per 3 months) at the University of Fukui Hospital from April 2006 to December 2017. Patients in whom no 12-lead ECGs were recorded before or during medical castration were available, and those who did not receive the therapy for >3 months were excluded from this study in advance. This study was approved by the Research Ethics Committee of the University of Fukui, and written consent was waived because of the retrospective design. The study complied with the Declaration of Helsinki.

Data Analysis

The electrocardiographic parameters were compared between those before and during the medical castration. The association of the electrocardiographic parameters with malignant arrhythmias was studied in this cohort. Malignant arrhythmias included TdP, ventricular tachycardia, VF, and asystole. Moreover, the plasma electrolyte levels and electrocardiographic findings were compared with the QT interval, before and during the medical castration. The QT intervals were measured in lead V2 using the tangent method for the determination of the QT end using a semiautomated digitizing program with electronic calipers by an experienced observer blinded to the clinical details in all subjects included in this study.^{9,10} The QT interval was determined from a 5-beat average during atrial fibrillation.¹⁰ The presence or absence of an abnormal ST-segment elevation in the right precordial leads, including a Brugada-type ECG, which was diagnosed by ST-segment elevation with a type 1 morphological feature of ≥ 2 mm in ≥ 1 leads among the V1 and/or V2 right precordial leads in the fourth intercostal space, was also evaluated.¹¹

Statistical Analysis

Continuous variables, except for the plasma potassium and calcium levels, are expressed as the mean \pm SD. Because of their nonnormality, the potassium and calcium plasma levels are given as the median (interquartile range), and outliers are defined as values above or below 1.5 times the interquartile range. Categorical variables are presented as the number and percentage. Differences in the parameters before and during the medical castration were analyzed using a paired *t*-test for a comparison. A Pearson correlation coefficient was used to determine the relation between the QTc interval and other variables. All statistical analyses were performed with SPSS (Statistical Package for the Social Sciences) version 20 software (IBM Inc,

Armonk, NY). A 2-sided $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the Cohort

A total of 149 patients with prostate cancer (mean age on starting of medical castration, 75 ± 6 years) who received the gonadotropin-releasing hormone, leuproreline ($n=96$ [65%]), gosereline ($n=36$ [24%]), or degarelix ($n=17$ [11%]), with antiandrogen drugs or androgen synthesis blockers (bicalutamide, flutamide, chlormadinone, enzalutamide, or abiraterone) ($n=103$ [69%]) or without antiandrogens ($n=46$ [31%]), were included in this study (Table 1). None had any malignant

arrhythmias or had taken any medications of relevance for QT prolongation before and during the medical castration.

Forty-six (31%) patients had radiation therapy. Twenty-eight patients (19%) had arrhythmias, including atrial fibrillation ($n=24$ [16%]), sick sinus syndrome ($n=1$ [1%]), paroxysmal supraventricular tachycardia ($n=1$ [1%]), premature ventricular contractions ($n=1$ [1%]), and atrioventricular block ($n=1$ [1%]) before medical castration. Twenty patients (13%) had cardiovascular diseases, including effort angina pectoris ($n=10$ [7%]), old myocardial infarctions ($n=8$ [5%]), and coronary spastic angina ($n=2$ [1%]), before the medical castration. Three patients (2%) had chronic, stable heart failure, but none had overt symptoms or signs of heart failure at the start of the medical castration therapy.

Table 1. Baseline Patient Characteristics, Therapy for Prostate Cancer, and Plasma Potassium and Calcium Levels Before and During the Therapy

Variable	Total	Torsade de Pointes and Ventricular Fibrillation	
	(n=149)	Present (n=2)	Absent (n=147)
Age at starting the medical castration, y	75 ± 6	70 ± 1	76 ± 6
Hypertension, n (%)	84 (56)	2 (100)	82 (56)
Diabetes mellitus, n (%)	35 (23)	2 (100)	33 (22)
Dyslipidemia, n (%)	29 (19)	0 (0)	29 (20)
Stroke/transient cerebral ischemic attack, n (%)	15 (10)	0 (0)	15 (10)
Chronic heart failure, n (%)	3 (2)	0 (0)	3 (2)
Ischemic heart disease, n (%)	20 (13)	0 (0)	20 (14)
Effort angina pectoris	10 (7)	0 (0)	10 (7)
Old myocardial infarction	8 (5)	0 (0)	8 (5)
Coronary spastic angina	2 (1)	0 (0)	2 (1)
Arrhythmias, n (%)	28 (19)	0 (0)	28 (19)
Atrial fibrillation	24 (16)	0 (0)	24 (16)
Sick sinus syndrome	1 (1)	0 (0)	1 (1)
Paroxysmal supraventricular tachycardia	1 (1)	0 (0)	1 (1)
Premature ventricular contraction	1 (1)	0 (0)	1 (1)
Atrioventricular block	1 (1)	0 (0)	1 (1)
Therapy for prostate cancer			
Gonadotropin-releasing hormone, n (%)			
Leuproreline	96 (62)	2 (100)	91 (62)
Gosereline	36 (24)	0 (0)	36 (24)
Degarelix	17 (11)	0 (0)	17 (12)
Antiandrogen drugs/androgen synthesis blockers, n (%)	103 (62)	1 (50)	102 (69)
Radiation therapy, n (%)	46 (30)	1 (50)	45 (31)
Plasma potassium level, mmol/L			
Before the therapy (n=126)	4.2 (4.0–4.4)	5.2	4.2 (4.0–4.4)
During the therapy (n=147)	4.2 (3.9–4.5)	3.8	4.2 (4.0–4.5)
Plasma calcium level, mg/dL			
Before the therapy (n=120)	9.1 (8.8–9.4)	10.3	9.0 (8.8–9.3)
During the therapy (n=145)	9.0 (8.6–9.2)	9.0	9.0 (9.0–9.3)

Values are reported as the mean \pm SD or number (percentage) of patients, unless otherwise noted. The plasma potassium and calcium levels are expressed as the median (interquartile range).

Change in the Electrocardiographic Parameters Attributable to Medical Castration

The 12-lead ECGs during the therapy were recorded at 25±22 months (range, 3–102 months) after the start of the therapy. The heart rate increased from 68±11 to 71±14 beats per minute ($P=0.006$), but the PQ interval and QRS duration were comparable before and during the therapy (Table 2). The QTc intervals prolonged with the medical castration in 119 (79.9%) patients, and the QT and QTc intervals during the therapy were longer than those before the therapy (both for $P<0.001$; Figure 1A). QTc intervals of ≥440 ms before the therapy and those of ≥500 ms during the therapy were found in 17% and 3% of the patients, respectively (Table 2). An increase in the QTc interval from the pretreatment value (Δ QTc) of >20 and >50 ms was found in 53% and 12% of the patients, respectively. There was a slightly positive correlation between the QTc interval before the therapy and the Δ QTc ($r=0.382$; $P<0.001$). No abnormal ST-segment elevation, including a Brugada-type ECG, was found in the right precordial leads before or during the therapy in any of the patients.

Medical Castration and Malignant Arrhythmias

Among the 149 patients, 2 (1.3%) with QT/QTc prolongation presented with TdP/VF during the therapy (Table 3). Those 2 patients had no structural heart disease, risk of cardiovascular disease, or family history of cardiac disease, including sudden death or QT prolongation (Table 4). They were confirmed to have no ischemic heart disease by a coronary angiogram or stress thallium-201 scintigram. No ventricular tachycardia or asystole was documented in any of the patients.

The first patient (a 71-year-old man) with metastatic prostate cancer (stage D) presented with a QT prolongation while receiving medical castration therapy, and the TdP/VF occurred at 6 months after starting the therapy (Table 4). Coronary angiography showed no

Table 2. Change in the Electrocardiographic Parameters in All Patients

Parameter	Before Therapy	During Therapy	P Value
Heart rate, /min	68±11	71±14	0.006
PQ interval, ms	184±88	181±30	0.725
QRS duration, ms	110±67	102±21	0.205
QT interval, ms	394±32	406±39	<0.001
QTc interval, ms	416±27	439±31	<0.001
QTc ≥440 ms, n (%)	25 (17)	121 (81)	<0.001
QTc ≥500 ms, n (%)	1 (1)	5 (3)	0.214

Values are reported as the mean±SD or number (percentage) of patients. QTc indicates corrected QT.

significant stenoses of the coronary arteries. He had no mutations related to long-QT syndrome. During the TdP/VF episode, the left ventricular (LV) wall motion diffusely decreased, with an LV ejection fraction of 21%. However, no regional LV wall motion abnormalities, suggesting Takotsubo cardiomyopathy, were found. The LV ejection fraction recovered to the level of that before the medical castration by 11 months. The QTc interval also improved after the discontinuation of the therapy. He had done well and had no VF recurrences during 38 months of follow-up.

The second patient (a 70-year-old man) with localized prostate cancer (stage B) was admitted to our hospital because of an operation for a renal cell carcinoma. His QT interval prolonged after starting the therapy, and the TdP/VF occurred 22 months after starting the therapy (Table 4 and Figure 2). At that time, the LV function was preserved, but the serum potassium level was low. Despite the correction of the serum potassium level, the QT prolongation did not completely improve. With cessation of the therapy, his QT interval had become normal. He had no VF recurrences during 72 months of follow-up.

Patients With and Without TdP/VF

Before the therapy, the patient characteristics, therapy for prostate cancer, and all electrocardiographic parameters were comparable between the patients with TdP/VF and those without TdP/VF (Tables 1 and 3). In 2 patients with TdP/VF, the QTc interval before the therapy was <440 ms. However, during the therapy, it was markedly prolonged, and the increase in the QTc interval before and during the therapy (Δ QTc) was >80 ms (Tables 3 and 4 and Figure 1B). On the other hand, in 147 patients without TdP/VF, 17% of the patients had a QTc interval ≥440 ms before the therapy. During the therapy, it was prolonged in 80% of the patients without TdP/VF. However, the prevalence of a Δ QTc of >50 and >60 ms was 11% and 5%, respectively, and a Δ QTc >80 ms was found in only 4 (3%) patients (Table 3 and Figure 1B). A Δ QTc >60 ms identified the development of TdP/VF with the highest accuracy (Table 5).

QT Interval and Plasma Electrolyte Levels

The median (interquartile range) of plasma level of the potassium was 4.2 (4.0–4.5) and 4.2 (4.0–4.4) mmol/L before and during the therapy, respectively. No close relationship was found between the QTc interval and plasma potassium level before and during the therapy (before: $r=0.057$, $P=0.526$; during: $r=0.184$, $P=0.025$). The median (interquartile range) of plasma level of the calcium was 9.1 (8.8–9.4) and 9.0 (8.7–9.3) mg/dL before and during the therapy, respectively. No close relationship was found between

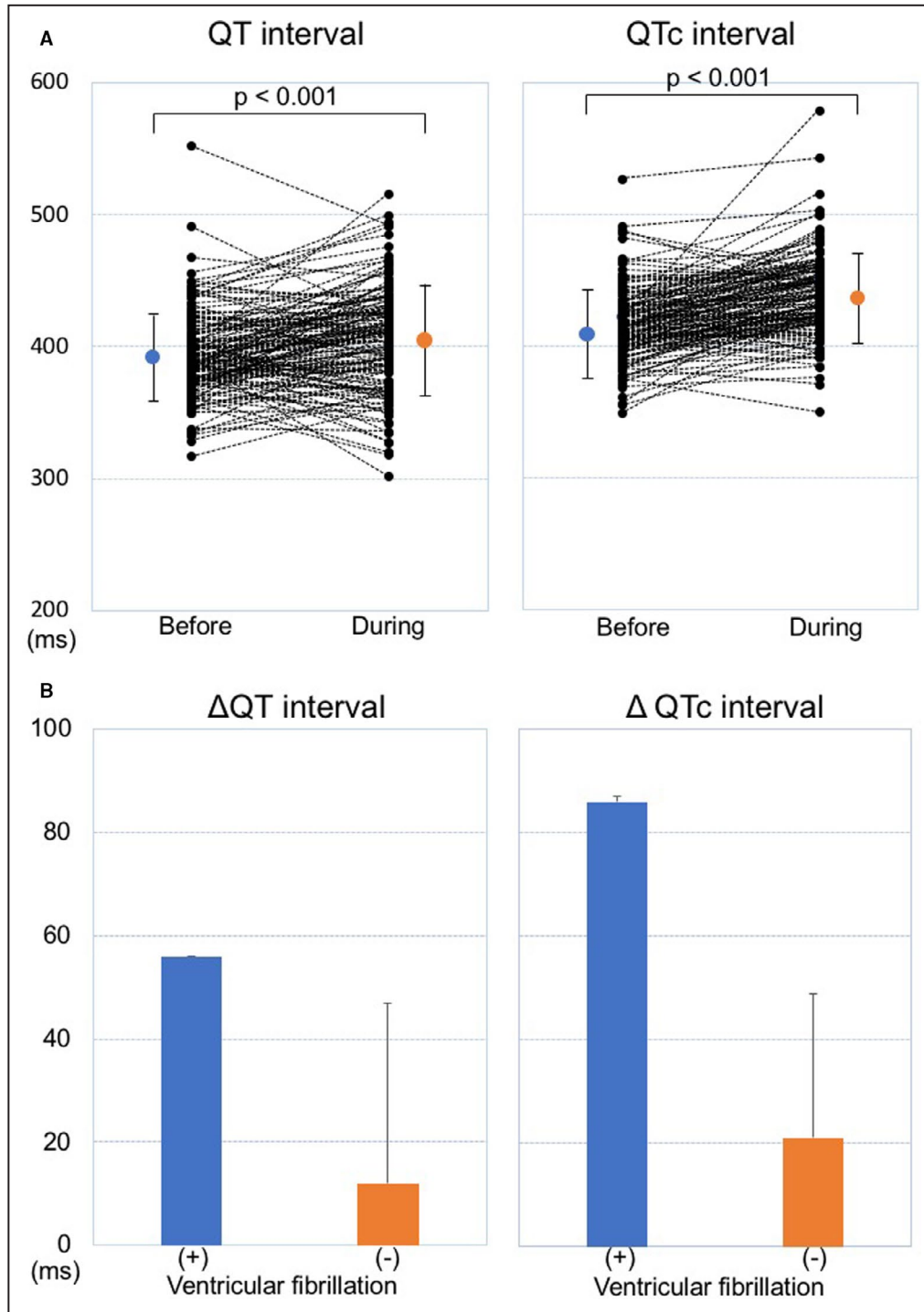


Figure 1. The QT and corrected QT (QTc) intervals during medical castration therapy. **A**, The QT and QTc intervals before and during the medical castration therapy. **B**, Increase in the QT (Δ QT) interval and increase in the QTc (Δ QTc) interval from the pretreatment value in patients who developed malignant arrhythmias during the medical castration therapy and those who did not. The QT and QTc intervals and those changes during medical castration therapy.

the QTc interval and plasma level of the calcium before the therapy ($r=0.144$; $P=0.113$). However, it was slightly correlated with the calcium level during the therapy ($r=0.253$; $P=0.002$).

QT Interval and Echocardiogram Parameters

Forty-four patients (30%) underwent an echocardiogram before and during the therapy. The LV

Table 3. Medical Castration and TdP/VF

Variable	TdP/VF	
	Present (n=2)	Absent (n=147)
Before therapy		
Heart rate, /min	57±0	67±11
PQ interval, ms	201±39	182±87
QRS duration, ms	119±23	109±68
QT interval, ms	424±18	393±32
QTc interval, ms	416±21	416±27
QTc interval ≥440 ms, n (%)	0 (0)	25 (17)
QTc interval ≥500 ms, n (%)	0 (0)	1 (1)
During therapy		
Heart rate, /min	68±5	71±14
PQ interval, ms	221±47	181±29
QRS duration, ms	113±24	102±21
QT interval, ms	480±20	405±38
QTc interval, ms	501±21	438±30
QTc interval ≥440 ms, n (%)	2 (100)	68 (46)
QTc interval ≥500 ms, n (%)	1 (50)	4 (3)
ΔQTc		
Incidence, n (%)		
>0 ms	2 (100)	117 (80)
>10 ms, n (%)	2 (100)	96 (65)
>20 ms, n (%)	2 (100)	77 (52)
>30 ms, n (%)	2 (100)	53 (36)
>40 ms, n (%)	2 (100)	34 (23)
>50 ms, n (%)	2 (100)	16 (11)
>60 ms, n (%)	2 (100)	8 (5)
>70 ms, n (%)	2 (100)	6 (4)
>80 ms, n (%)	2 (100)	4 (3)

Values are reported as the mean±SD or number (percentage) of patients. ΔQTc indicates increase in the QTc interval from the pretreatment value; QTc, corrected QT; TdP, torsade de pointes; and VF, ventricular fibrillation.

end-diastolic diameter during the therapy was 49±5 mm, which was comparable to that before the therapy (47±5 mm; $P=0.084$). The LV ejection fraction during the therapy was also comparable to that before the therapy (65%±13% versus 65%±7%; $P=0.867$).

No close correlation was found between the QTc interval before the therapy and the LV diastolic diameter ($r=0.078$; $P=0.616$) or LV ejection fraction ($r=0.046$; $P=0.769$). However, the QTc interval during the therapy was slightly correlated with the LV diastolic diameter ($r=0.308$; $P=0.042$) or LV ejection fraction ($r=0.334$; $P=0.027$) during the therapy.

Among 44 patients who underwent echocardiography before and during the therapy, 1 had LV systolic dysfunction with an LV ejection fraction of <50% before the therapy. No further deterioration of the LV systolic dysfunction was found during the therapy. Another 4 (9.3%) patients newly presented with LV systolic

dysfunction during the therapy, and 1 of them developed TdP/VF during the therapy.

Prognosis of the Patients

During the observation period, 52 patients (mean age, 81±8 years) died: The most common cause of death ($n=27$ [52%]) was prostate cancer. The second most common cause of death was attributable to other cancers ($n=10$ [19%]). Other causes of death included infectious disease ($n=8$ [15%]: pneumonia [$n=6$], pulmonary tuberculosis [$n=1$], and urinary tract infections [$n=1$]), cerebral infarctions ($n=2$ [4%]), respiratory failure ($n=1$ [2%]), and senile decay ($n=4$ [8%]). None had any sudden death highly suspicious of TdP/VF.

DISCUSSION

Major Findings

The results of this study that included 149 patient with prostate cancer receiving medical castration demonstrated the following findings: (1) medical castration prolonged the QTc interval in 79.9% of the patients; (2) TdP/VF occurred in 2 (1.3%) patients who had no structural heart disease or any arrhythmias, and it occurred later (≥6 months after receiving medical castration); (3) the QT prolongation recovered with the discontinuation of the medical castration; (4) before the therapy, all electrocardiographic parameters were comparable between the patients with TdP/VF and those without TdP/VF; and (5) during the therapy, the ΔQTc was longer in the patients with TdP/VF than in those without TdP/VF, and the incidence of TdP/VF was higher in patients with a ΔQTc of >50 ms.

These findings indicated that medical castration prolonged the QT and QTc intervals in most patients with prostate cancer and could rarely cause TdP/VF. Much attention should be paid to the QTc interval, especially the ΔQTc, throughout all periods of medical castration to prevent malignant arrhythmias in all patients.

Prolonged QT/QTc Intervals and TdP/VF During Medical Castration

Sex steroid hormones, including testosterone, play an important role in cardiac repolarization and the control of the QT intervals.^{12–14} The sex differences in the sex hormones are considered to be the main reason for the sex difference of long-QT syndrome and malignant arrhythmias. Medical castration, the mainstay treatment in patients with advanced prostate cancer, strongly suppresses testosterone,² and could affect the QT interval: castrated men could exhibit a longer duration of the QTc interval than noncastrated men,⁵ and medical and surgical castration results in prolonged QT intervals

Table 4. Two Patients Who Developed TdP/VF During Medical Castration Therapy

Patient No.	Age, y	Medical Castration Therapy	Electrocardiographic Parameters				Echocardiographic Parameters				Plasma Electrolyte Levels		
			Before Therapy	During Therapy	After Cessation of Therapy		Before Therapy	During Therapy		Before Therapy	During Therapy		
1	71	Leuprorelin, bicalutamide	HR, /min	57	71	80	LVEF, %	57	21	Potassium, mEq/L	4.6	4.5	
			QT, ms	438	494	408	LVDD, mm	57	66	Calcium, mg/dL	9.4	8.7	
			QTc, ms	431	516	472	LVDs, mm	40	60	Magnesium, mg/dL	NA	NA	
			Δ QTc, ms		+85								
2	70	Leuprorelin, brachytherapy	HR, /min	57	64	69	LVEF, %	71	70	Potassium, mEq/L	5.8	3.1	
			QT, ms	410	466	410	LVDD, mm	50	44	Calcium, mg/dL	11.1	9.2	
			QTc, ms	401	482	432	LVDs, mm	30	26	Magnesium, mg/dL	NA	2.1	
			Δ QTc, ms		+81								

Δ QTc indicates increase in the QTc interval from the pretreatment value; HR, heart rate; LVDD, left ventricular end-diastolic diameter; LVEF, left ventricular end-systolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; NA, not available; QTc, corrected QT; TdP, torsade de pointes; and VF, ventricular fibrillation.

in castrated men.¹⁵ Recently, the incidence of TdP and sudden death attributable to medical castration has been examined from the international pharmacovigilance database VigiBase (n=6 560 565 individual case safety reports).¹⁶ TdP and sudden death were found in 68 and 99 cases, respectively, indicating that medical castration could cause TdP/VF or sudden death. However, some patients received medical castration because of prostatism and androgenic alopecia, not prostate cancer. Because those data were obtained from uncontrolled sources,¹⁶ the detailed information on the electrocardiographic measurements is lacking. Furthermore, the precise causes of sudden death in patients receiving medical castration for prostate cancer might be unclear. In that report,¹⁶ sudden death occurred 0.25 to 90 days after starting the medical castration. Some cases of sudden death that occurred shortly after starting the medical castration might not have been attributable to TdP/VF.

In the present study, for the patients with prostate cancer receiving medical castration, we examined the incidence and characteristics of QT/QTc prolongation and the incidence and mode of the onset of TdP/VF. In patients with prostate cancer, prolongation of the QT and QTc interval developed in \approx 80% during medical castration. Furthermore, although rare (2 patients [1.3%]), TdP/VF could occur during the therapy. It should be specially noted that TdP/VF could occur in patients with no structural heart disease or risk of QT prolongation before the therapy, and that it could occur several months after the initiation of the therapy. Our results indicated that special attention should be paid to the prolongation of the QT and QTc intervals throughout all periods of the medical castration in all patients with prostate cancer receiving this therapy.

Predictors of TdP/VF During Medical Castration

Several risk factors for drug-induced TdP/VF have been reported.^{17–21} In the present study, the pretreatment QTc intervals \geq 440 ms and those \geq 500 ms, known as risk factors for drug-induced TdP/VF,^{17,18,21} in patients with TdP/VF were similar to those in patients without TdP/VF. The incidence of a QTc \geq 500 ms was also comparable between these 2 groups. However, the magnitude of the Δ QTc differed between these 2 groups. In patients with TdP/VF, the Δ QTc was $>$ 80 ms. On the contrary, in patients without TdP/VF, the prevalence of a Δ QTc of $>$ 50 ms was found in only 11% of the patients. Previous studies reported that a Δ QTc of $>$ 60 ms was a predictor of TdP/VF in patients receiving QT-prolonging agents.^{18–20} In our study, the patients were all men, and the age on starting the therapy was 75 ± 6 years (range, 62–92 years), which seems to be older than that in the previous

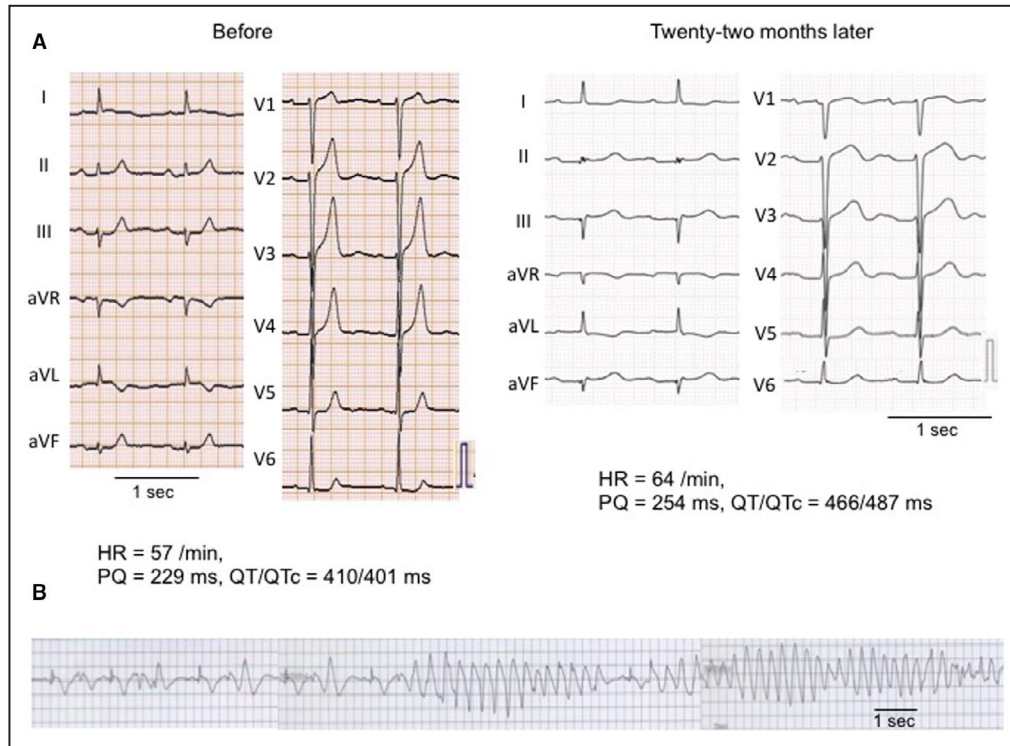


Figure 2. Representative ECG recordings obtained in a patient who developed torsade de pointes and ventricular fibrillation during medical castration therapy.

A, Twelve-lead ECGs before and 22 months after the medical castration. **B**, Tracings of the bedside continuous single-lead ECG monitoring. Torsade de pointes and ventricular fibrillation spontaneously occurred 22 months after the medical castration. HR indicates heart rate; and QTc, corrected QT.

studies^{19,20} including younger and/or female subjects. It is well known that, because the level of testosterone gradually decreases with age in adult men, the QTc interval in men gradually lengthens with aging.¹⁴ Therefore, there is a possibility that the QTc interval before the therapy was longer in our patients than in those of the previous studies including young subjects and/or women. We think that, in aged patients who have relatively long-QTc intervals before the therapy, a smaller increase in the QTc interval while receiving QT-prolonging agents might become a risk for TdP/VF. That might be the reason why the magnitude of the Δ QTc for predicting TdP/VF was smaller in our study than in the previous studies. We believe that, in aged patients receiving QT-prolonging agents, as in our patients, a stricter predictor, a Δ QTc >50 ms, should be used to predict TdP/VF, and the discontinuation of the therapy should be considered.

Heart failure with a reduced LV ejection fraction¹⁹ and hypokalemia²¹ are well-known risk factors for TdP. In the present study, during the TdP/VF during the medical castration, one patient presented with LV systolic dysfunction, and the other had hypokalemia. These circumstances might facilitate the TdP/VF occurrence. In this study, the QTc interval during the medical castration correlated with the LV diastolic diameter and LV ejection fraction, which might have indicated that the medical castration might damage the cardiac myocytes and cause QT prolongation.^{22,23} Therefore, during medical castration, it is also important to evaluate the cardiac function and avoid an electrolyte imbalance. When patients develop TdP/VF during medical castration, a prompt cessation of the therapy and a correction of the electrolyte disorder, if it exists, are indispensable to avoid recurrences of TdP/VF and sudden death.

Table 5. Sensitivity, Specificity, and Predictive Accuracy of the Criteria for TdP/VF During Medical Castration

Criterion	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
Δ QTc interval >50 ms	11.1	100	100	89.1
Δ QTc interval >60 ms	20.0	100	100	94.6

Δ QTc indicates increase in the corrected QT interval from the pretreatment value; TdP, torsade de pointes; and VF, ventricular fibrillation.

Study Limitations

First, this study was a single-center nonrandomized study, and further prospective studies are needed to investigate the role of QT prolongation in malignant arrhythmias. Second, the timing of obtaining an ECG during the therapy varied. Third, drug-induced long-QT syndrome might have been related as a carrier of congenital long-QT syndrome disease-causing mutations. Fourth, the QT intervals were measured in lead V2. The QT interval is preferably measured in lead II or V5 for long-QT syndrome.²⁴ We initially attempted to determine that in those 2 leads. However, we could not precisely do that in those 2 leads because of the difficulty in recognizing the end of the T wave in some patients. Fifth, the plasma testosterone levels were not measured. Finally, because of the small number of patients with TdP/VF (n=2), no statistical comparisons between the patients with TdP/VF and those without could be completed.

ARTICLE INFORMATION

Received April 26, 2020; accepted November 16, 2020.

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Acknowledgments

We thank Professor Ryosuke Fujita for his critical suggestions about the statistical analyses. We also thank John Martin for his help in the preparation of the manuscript.

Sources of Funding

This work was supported in part by the Akaeda Medical Research Foundation research grant (to Dr Hasegawa) and Grant-in-Aid for Young Scientists (Japan Society for the Promotion of Science KAKENHI, JP19K19553) (to Dr Hasegawa).

Disclosures

None.

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