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Clinical report

Docetaxel does not impair cardiac autonomic function in breast cancer patients previously treated with anthracyclines

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The effects of docetaxel treatment on autonomic cardiac function was studied with 24-h ECG recordings in breast cancer patients pretreated with anthracyclines. Twenty-four women were evaluated before docetaxel treatment and after 3–4 courses of docetaxel 100 mg/m^2. The heart rate, cardiac extrasystoles and heart rate variability (HRV) in both the time and frequency domain were assessed from 24-h ECG recordings. The acute effects of docetaxel were calculated from 1-h recordings immediately prior to, during and after infusion. Long-term effects were evaluated from 24-h recordings performed before treatment and after 3–4 courses of docetaxel. There was no increase in the number of cardiac extrasystoles during docetaxel infusion. The number of ventricular extrasystoles decreased from 14 (23) to 7 (14) during and 5 (10) after the first infusion (p=0.02). The heart rate, HRV and extrasystoles were similar before and after 3–4 courses of docetaxel. The treatment did not abolish circadian variability of the heart rate. Docetaxel did not deteriorate autonomic cardiac function. In conclusion, our findings suggest that docetaxel does not have harmful cumulative effects on autonomic control of the heart and is therefore unlikely to be cardiotoxic. [© 2002 Lippincott Williams & Wilkins.]

Keywords: Autonomic nervous system, cardiotoxicity, chemotherapy, docetaxel, heart rate variability.

Introduction

Taxoids, paclitaxel and docetaxel, are new chemotherapeutics used in the treatment of cancer. Docetaxel is the first drug shown to have superior effect compared to anthracyclines in the treatment of advanced breast cancer.[1] Docetaxel is active even in breast cancer patients with anthracycline-resistant disease.[2] It has a different profile of side effects compared to paclitaxel, which has been associated with significant peripheral neuropathy and cardiac side effects as well as few cardiac deaths.[3,4] Moreover, simultaneous administration of doxorubicin and paclitaxel has increased the risk of cardiotoxicity and the incidence of congestive heart failure up to 20%.[5,6] Recent studies imply that cardiac side effects of paclitaxel–anthracycline combinations are related to the cumulative anthracycline dose.[7] Docetaxel treatment has not been associated with increased cardiac toxicity.[8] However, experimental data suggest that adding a taxane to doxorubicin enhances formation of cardiotoxic metabolites.[9,10]

Our previous studies showed that paclitaxel impairs heart rate variability (HRV) in 24-h ECG recordings. The circadian fluctuation of heart rate diminished and the ratio between low-frequency (LF) and high-frequency (HF) HRV decreased after two courses of paclitaxel.[11] The findings suggest that paclitaxel has an adverse effect on cardiovascular autonomic regulation. Little is known of the influences of docetaxel on autonomic control of the heart. *In vitro* studies on animals imply that docetaxel lacks cardiodepressant and arrhythmogenic effects.[12] Changes in cardiac autonomic function are commonly observed in congestive heart disease.[13] It has been suggested that changes in HRV precede left ventricular systolic dysfunction and heart failure in cancer patients receiving cardiotoxic chemotherapy.[13] Therefore, diminished HRV may be the first sign of cardiotoxicity.

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The aim of this study was to assess the effects of docetaxel treatment on autonomic cardiac function with 24-h ECG recordings.

Patients and methods

Twenty-four women who were treated with docetaxel for metastatic breast cancer after anthracycline therapy were included in the study. All the patients were previously treated with epirubicin and none of them had clinical signs of peripheral neuropathy at the beginning of the study. Two patients had diabetes, one of these also had hypertension. Altogether five patients were diagnosed as having a cardiovascular disease, three of them had hypertension, one had aortic valve insufficiency and one had atrial septal defect. Docetaxel was given every 3 weeks as 1-h infusion. Dexamethasone 8 mg was given the night before treatment and b.i.d for 4 days. Patient characteristics and details of treatment doses are given in Table 1. Altogether eight out of 24 patients received four courses of docetaxel with a full dose of 100 mg/m^2. Causes for dose reductions are presented in Table 2. The most common reasons for dose reduction were bone marrow suppression, infection and heavy pretreatment. The dose was most often reduced by 20–30% with a range of 6–34%. There were four patients who received reduced doses from the onset of treatment due to extensive prior chemotherapy. Their dose reductions ranged from 20 to 32%. The study was approved by the Ethics Committee of the Turku University and all participants gave informed consent.

Table 2. Causes for dose reduction or discontinuation of docetaxel treatment

Side effects	No. of patients
Hematological side effects	6
Infection	4
Elevated liver enzymes	3
Heavily pretreated	4
Skin reactions	3
Decreased performance status	1

Five out of 16 patients receiving a reduced dose suffered from two concomitant side effects leading to dose adjustment

A 24-h ambulatory ECG was recorded from all patients during normal activities with their normal sleep/wake rhythm. The 24-h ECG was recorded before the first docetaxel course and within 24 h of the fourth course.

The acute effects of docetaxel on autonomic control of the heart were assessed from the first recording by comparing the heart rate and HRV from 1-h recordings immediately prior to, during and after docetaxel infusion. The long-term effects of docetaxel on HRV were determined by comparing HRV measured prior to docetaxel therapy with HRV after 3 or 4 courses of treatment, both from 1- and 24-h recordings. HRV of the pretreatment ECG recording, which was obtained within 48 h before the first infusion, was compared to recordings before or after the fourth course to assess the effect of docetaxel treatment on circadian variability of HRV.

Table 1. Patient characteristics

Characteristics	*N*
No. of patients	24
Age [years (median, range)]	50 (39–60)
Cardiovascular disease	5
Diabetes	2
Prior radiotherapy	
to chest wall	18
to left side	14
Prior anthracylines	
Cumulative epirubicin [mg/m^2 (median, range)]	505 (120–990)
No. patients receiving 4 courses with a dose of 100 mg/m^2	8
No. patients receiving 3 courses with a dose of 100 mg/m^2	2
No. patients receiving 2 courses with a dose of 100 mg/m^2	5
No. patients receiving 1 course with a dose of 100 mg/m^2	5
No. patients receiving a reduced dose throughout the treatment	4
Docetaxel dose/cycle	
first cycle [mg/m^2 (median, range)]	99.5 (60–100)
second cycle [mg/m^2 (median, range)]	97 (57–100)
third cycle [mg/m^2 (median, range)]	95 (57–100)
fourth cycle [mg/m^2 (median, range)]	78 (57–100)

The two-channel recordings were analyzed with MARS 8000 arrhythmia review station (Marquette Electronics, Milwaukee, WI). HRV was assessed in frequency and time domain. QT time was manually measured from ECG prints chosen from 1-h recordings before, during and after the first docetaxel infusion. The mean of three QT times was calculated and used in statistical comparisons.

Periodic HRV

Spectral analysis was used to quantify the periodic components of HRV. Spectral power of HRV was calculated with fast Fourier transformation algorithm. Power spectra was quantified in four frequency bands: very low-frequency power (VLF) from 0.0033 to 0.04 Hz, LF power from 0.04 to 0.15 Hz, HF from 0.15 to 0.40 Hz and variability related to blood pressure oscillations from 0.09 to 0.11 Hz. VLF variability is associated with sympathetic vasomotor regulation. LF variability relates to baroreflex activity, and is modulated by both sympathetic and parasympathetic control. HF variability is vagally mediated and reflects respiratory sinus arrhythmia.[14] The LF/HF ratio between spectra was also calculated.

Time domain analysis of HRV

Mean RR interval, SD of RR intervals (SDNN), root mean square of successive differences in RR intervals (RMSSD) and the percentage of successive RR interval differences greater than 50 ms (NN50) were calculated. SDNN is used to assess overall variability in heart rate, whereas RMSSD reflects beat-to-beat variability. Twenty-four-hour ECGs have shown that NN50 is a sensitive way to monitor parasympathetic activity and detect early parasympathetic damage.[15]

Statistical analyses

First, analysis of variance for repeated measurements was performed using the BMDP statistical package (2V) to study acute changes and circadian changes in the heart rate, HRV and QT time. Log transformations were performed for non-Gaussian data. Long-term effects were assessed with the Wilcoxon signed rank-sum test. The data are shown as mean (SD).

Results

The acute effects

The mean RR interval before docetaxel was 666 (67) ms, and it increased to 716 (73) ms during the infusion and remained stable after the infusion 720 (89) ms (p=0.01). HRV did not change during docetaxel infusion. Furthermore, there was no increase in cardiac extrasystoles during docetaxel infusion. However, the number of ventricular extrasystoles decreased from 14 (23) during 1 h before the first infusion to 7 (14) during and 5 (10) after the infusion (p=0.02). The number of supraventricular extrasystoles was 6 (13) before, 4 (7) during and 5 (14) after the infusion (p=0.87). The QT time increased from 18.3 (1.4) ms before to 19.3 (1.7) ms during infusion and remained 19.1 (1.7) ms after the first docetaxel infusion (p=0.02). This increase is probably connected with the lengthening of the RR interval.

Long-term effects

The heart rate, HRV and the number of cardiac extrasystoles remained similar before docetaxel treatment and after 3–4 courses of docetaxel as measured from both 1- and 24-h recordings (Table 3). The LF/HF ratio decreased from 4.50 (1.67) to 2.98 (1.45)

Table 3. Long-term effects of docetaxel on the heart measured as 24-h RR interval and HRV during the day of the first course compared to the day of third or fourth course of docetaxel [mean (SD)]

	Day of first course	Day of third/fourth course	*P*
RR interval (ms)	713 (71)	698 (94)	0.51
Ventricular extrasystoles (*N*)	131 (287)	70 (185)	0.97
Supraventricular extrasystoles (*N*)	60 (136)	47 (53)	0.70
HRV			
SDNN (ms)	114.5 (30.4)	114.4 (54.0)	0.78
NN50	1.96 (2.65)	6.56 (13.46)	0.35
HF (ms^2)	61 (57)	129 (211)	0.59
LF (ms^2)	228 (222)	251 (248)	0.98
VLF (ms^2)	455 (307)	492 (407)	0.72

Table 4. The effect of circadian variation on RR interval and HRV before and after 3–4 courses of docetaxel [mean (SD)]

	Awake	Sleep	*p*
RR interval (ms)			
before	659 (40)	835 (140)	<0.0001
after	746 (104)	939 (151)	
HF power (ms^2)			
before	48 (43)	95 (115)	<0.0001
after	109 (106)	326 (245)	
LF power (ms^2)			
before	226 (233)	237 (306)	0.07
after	255 (225)	746 (709)	
VLF power (ms^2)			
before	411 (240)	430 (477)	0.32
after	511 (267)	1472 (1225)	

p: the difference between awake and sleep recordings. There was no significant treatment effect on any of the variables.

($p=0.002$) when measured from 1-h recording, but 24-h recordings showed no significant change [3.9 (1.0) versus 3.2 (1.7), $p=0.18$]. The LF/HF ratio measured from 24-h recordings is likely to assess the balance between sympathetic and parasympathetic systems better than a short recording.

Circadian variability

There was a significant difference in HRV between awake and sleep recordings both before and after 3–4 courses of docetaxel. This shows that docetaxel does not impair circadian variation of autonomic control (Table 4).

Discussion

We found that docetaxel treatment did not impair HRV or increase the number of extrasystoles in previously anthracycline-treated breast cancer patients. These findings support the view that docetaxel does not cause cardiotoxicity.

The spectral measures of HRV change early in the course of ventricular systolic dysfunction.[16] Therefore, the assessment of HRV has been proposed to identify patients at risk of development of chemotherapy induced congestive heart failure.[17] Impaired HRV and left diastolic dysfunction has been reported in anthracycline-treated asymptomatic women with normal systolic function.[13] Thus, changes in HRV may be an early sign of cardiotoxicity. Further, changes in HRV as assessed with 24-h ECG are widely accepted to predict life-threatening cardiac arrhythmias[18] and mortality[19] in patients with coronary artery disease. We used this methodology to study the cumulative effect of docetaxel on autonomic cardiac control and found no harmful effects after 3–4 courses of docetaxel in previously anthracycline-treated breast cancer patients. The finding of this study is in line with our clinical findings of patients with 6-month docetaxel treatment and median follow-up of greater than 10 months. In contrast to earlier case control studies on the effect of chemotherapy on autonomic cardiac function, our patients were evaluated for the first time already before docetaxel treatment.

Decreased HRV has been reported in a majority of asymptomatic anthracycline-treated patients with normal left ventricular systolic function when compared to healthy control subjects.[13] Our patients had low pretreatment values of HRV, but a normal circadian variation in heart rate although all of them were pretreated with anthracyclines. The preserved circadian fluctuation in the heart rate suggests that chemotherapy has not totally eliminated parasympathetic cardiac control. Besides neuropathy, the observed impairment of HRV may be related to direct myocardial toxicity due to anthracyclines.

Autonomic cardiac function of these patients did not further deteriorate during the study even if the disease was progressive or non-responsive in several of the patients. There was a small increase in QT time during docetaxel infusion, possibly relating to the change in RR interval. An increase in RR interval is not associated with autonomic neuropathy and can rather be considered to protect from extrasystoles. Indeed, docetaxel treatment did not increase the number of ventricular or supraventricular extrasystoles.

In a previous study we found that systolic blood pressure oscillations diminished at rest and the blood pressure increased in response to orthostatic stress after docetaxel therapy. However, the autonomic function tests did not reveal any significant

impairment in baroreflex sensitivity or cardiac autonomic control.[20] The observed changes were related to altered cardiovascular homeostasis rather than peripheral sympathetic neuropathy. The effects of paclitaxel on autonomic function tests were not significantly more harmful.[21] In contrast to the observations from the autonomic function tests, we found that paclitaxel significantly decreases the LF/HF ratio and impairs circadian variability of the heart rate in 24-h ECG recordings.[11] This was clearly not the case with docetaxel as shown in this study. Blunted circadian rhythm of spectral measures of HRV and reduced LF/HF ratio have been shown to predict cardiac mortality.[19,22] Our previous and present results suggest that circadian fluctuation of HRV may be more sensitive than autonomic function tests in detecting cardiac side effects caused by chemotherapeutic agents.

Conclusion

HRV measured from ECG recordings before docetaxel therapy and immediately before or after the fourth docetaxel course remained unchanged. Thus, docetaxel did not have harmful cumulative effects on autonomic control of the heart and is therefore unlikely to have clinically significant cardiotoxicity.

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