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Original article

Effect of epirubicin-based chemotherapy and dexrazoxane supplementation on QT dispersion in non-Hodgkin lymphoma patients

Fabio Galetta [a,*], Ferdinando Franzoni [a], Giulia Cervetti [b], Nadia Cecconi [b], Angelo Carpi [c], Mario Petrini [b], Gino Santoro [a]

[a] Department of Internal Medicine, University of Pisa School of Medicine, Via Roma, 67, 56126 Pisa, Italy
[b] Department of Hematology, University of Pisa School of Medicine, Via Roma, 67, 56126 Pisa, Italy
[c] Department of Reproduction and Ageing, University of Pisa School of Medicine, Via Roma, 67, 56126 Pisa, Italy

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Abstract

Background and objective. – Aim of the present study was to assess the effect of epirubicin-based chemotherapy on QT interval dispersion in patients with aggressive non-Hodgkin lymphoma (NHL), and the effect of dexrazoxane supplementation.

Prolongation of QT dispersion may not only represent a sensitive tool in identifying the first sign of anthracycline-induced cardiotoxicity, but it may serve also in identifying patients who are at risk of arrhythmic events.

Methods. – Twenty untreated patients, ≤60 years of age with newly-diagnosed aggressive NHL, eligible for a treatment with epirubicin-based chemotherapy were selected for the study. The patients were randomly allocated in two subgroups ($N = 10$) to receive or not dexrazoxane hydrochloride (400 mg/m^2) after epirubicin infusion. The patients underwent 12-lead electrocardiogram (ECG) before and after epirubicin infusion and after dexrazoxane supplementation. QT dispersion was defined as the difference between the maximum and the minimum QT interval occurring in any of the 12 ECG leads, corrected (QTc) for heart rate.

Results. – All the 20 patients showed increased QT dispersion (44.3 ± 8.4 vs. 68.4 ± 11.4 ms, $P < 0.001$) and QTc dispersion (46.2 ± 6.2 vs. 72.2 ± 8.4, $P < 0.001$) after chemotherapy infusion. The 10 patients who underwent supplementation with dexrazoxane exhibited a significant reduction of QT dispersion (67.4 ± 8.1 vs. 49.5 ± 4.2 ms, $P < 0.001$) and QTc dispersion (71.2 ± .7 vs. 51.4 ± 4.3 ms, $P < 0.001$), while the 10 patients not supplemented with dexrazoxane did not (QT dispersion: 69.3 ± 7.6 vs. 64.2 ± 6.9 ms; QTc dispersion: 72.8 ± 8.1 vs. 67.3 ± 7.2 ms, ns).

Conclusions. – Epirubicin-based chemotherapy causes an early increase of the QT and QTc dispersion, which is attenuated by dexrazoxane supplementation. Therefore, dexrazoxane can reduce the arrhythmic risk in patients treated with epirubicin.

Keywords: QT dispersion; Anthracycline; Epirubicin; Dexrazoxane; Lymphoma

1. Introduction

The clinical usefulness of anthracyclines, which have been shown to be effective in treating various tumors, is limited by their cardiotoxicity. Congestive heart failure, cardiomyopathy and electrophysiological alterations have been observed following anthracycline administration in both experimental animals and patients [1].

Some authors showed that anthracyclines cause significant changes in myocardial depolarization and repolarization with prolongation of QTc, increased QT dispersion and the development of ventricular late potentials [2].

In particular, increased QT dispersion, defined as an increase in inter-lead QT interval variability on the surface electrocardiogram (ECG), has been linked to an increased heterogeneity of ventricular repolarization and has been considered as

* Corresponding author. Tel.: +39 050 99 3373; fax: +39 050 55 3414.
E-mail address: fgaletta@med.unipi.it (F. Galetta).

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a non-invasive marker of risk for clinically important ventricular arrhythmias and cardiac mortality in individuals with and without heart disease [3–7].

Recently, dexrazoxane has been proposed to be the only clinically proved cardioprotective agent against anthracycline induced cardiotoxicity. The drug is thought to attenuate cardiac toxicity by binding to free and bound iron, thus reducing the formation of anthracycline–iron complexes and the generation of free radicals which are toxic to cardiac tissue [8,9].

Aim of the present study was to assess the effect of epirubicin-based chemotherapy on QT dispersion in patients with non-Hodgkin lymphoma (NHL) and its possible improvement by dexrazoxane supplementation.

2. Methods

2.1. Patients

The study was conducted between June 2001 and September 2002 in the Hematology Unit of our institution. Twenty patients ≤60 years of age with newly-diagnosed NHL, scheduled to receive ProMECEcytaBOM chemotherapy, were studied. Included subjects had an adequate performance status (score of 0–3 according to the criteria of the Eastern Cooperative Oncology Group [ECOG]) [10]. We excluded patients who had active cardiac disease, including myocardial infarction occurring within 12 months, active angina pectoris, symptomatic valvular heart disease, or uncontrolled congestive heart failure. The baseline resting left ventricular ejection fraction had to be greater than or equal to 50%.

The ProMECEcytaBOM chemotherapy consisted of intravenous epirubicin (a bolus dose of 40 mg/m^2), followed by intravenous cyclophosphamide (650 mg/m^2) and intravenous etoposide (120 mg/m^2) on day 1, and intravenous prednisolone (60 mg/m^2) on days 1–14. Vincristine (1.4 mg/m^2, maximum 2), methotrexate (120 mg/m^2), aracytin (300 mg/m^2) and bleomicin (5 mg/m^2) were given intravenously on day 8. The cycle was repeated every 3 weeks. The patients were randomly assigned in two groups ($N = 10$) to receive or not dexrazoxane hydrochloride (Cardioxane, Chiron, Amsterdam, The Netherlands), given intravenously (400 mg/m^2) over 15 min, immediately after the cyclophosphamide–epirubicin infusion.

All the patients underwent 12-lead ECG and echocardiogram before and after cyclophosphamide–epirubicin infusion, and after dexrazoxane supplementation.

The ethical Committee of Central Hospital approved the study and a written consent was obtained from each patient.

2.2. Measurement of QT interval and QT dispersion

ECGs with a duration of 10 s were recorded with a Cardiovit CS-100 (Schiller-AG, Baar, Switzerland), using the same system at 25 mm/s paper speed and standardized at 0.1 mV/mm. QT intervals were measured manually in all the 12 leads in blinded fashion from the onset of the QRS complex to the end of the T wave, as previously described in [11,12]. When U waves were present, the QT interval was measured to the nadir of the trough between the T and U waves. If the end of the T wave could not be identified, the lead was not included. Three consecutive QT intervals were measured and averaged for each lead. A minimum of nine leads in which the QT interval could be measured was required for QT dispersion to be determined. QT dispersion was defined as the difference between the longest and shortest QT intervals. With use of Bazett's formula, QT dispersion was corrected (QTc) for heart rate. Because of the known difficulties concerning definition of the end of the T wave, all ECGs were analyzed twice by two observers. Intraobserver and interobserver variability for QT dispersion measurements were < 3% and < 5%, respectively. Differences were resolved by consensus.

2.3. Statistical analysis

Results are expressed as mean ± standard deviation (S.D.). The one-way analysis of variance (ANOVA) was used. Differences were considered significant at P value < 0.05. All statistical procedures and curve fitting for statistical analysis were performed by means of personal computer programs (StatView, Abacus Concepts, Inc., SAS Institute, Cary, NC).

3. Results

Clinical characteristics of the study populations are presented in Table 1.

The echocardiographic parameters, such as left ventricular diastolic diameter, posterior wall diastolic thickness, and left ventricular ejection fraction at baseline and after chemotherapy, were normal in all patients.

All the patients showed increased QT dispersion (44.3 ± 8.4 vs. 68.4 ± 11.4 ms, $P < 0.001$) and QTc dispersion (46.2 ± 6.2 vs. 72.42 ± 8.4 ms, $P < 0.001$) after epirubicin-based chemotherapy. Patients who underwent supplementation with dexrazoxane hydrochloride exhibited a significant attenuation of QT dispersion (67.4 ± 8.1 vs. 49.5 ± 4.2 ms, $P < 0.001$) and QTc dispersion (71.2 ± 7.7 vs. 51.4 ± 4.3 ms, $P < 0.001$) in

Table 1
Patients and lymphoma characteristics

Age (years)	54 ± 7
Sex (M/F)	11/9
LDH (U/l)	642 ± 146
Histology	
DLCL	18
Anaplastic CD30+	2
IPI	
0–2	17
>2	3
Stage	
II	11
III	6
IV	3
Response rate (%)	88
Complete response	87
Partial response	13
Failure free survival (months)	28 ± 11

DLCL = diffuse large cell lymphoma; IPI = International Prognostic Index.

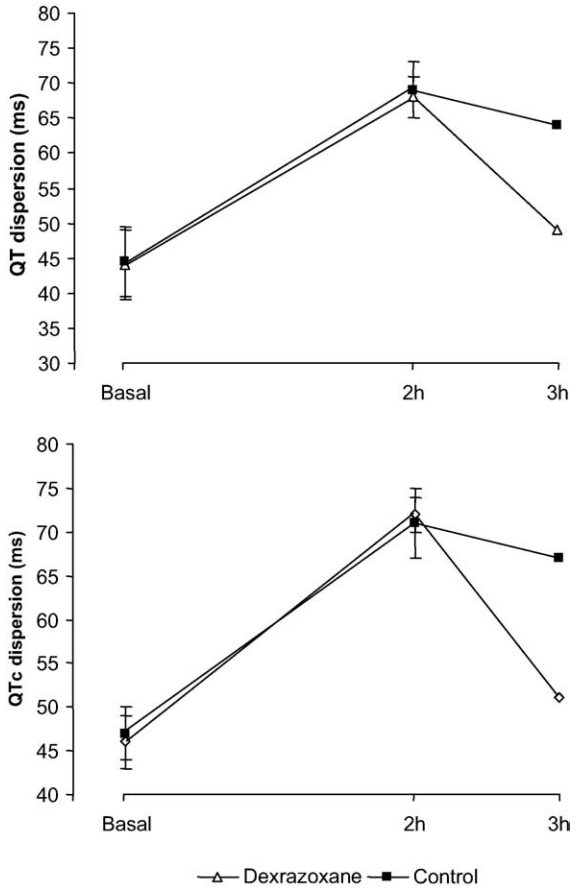

Fig. 1. Graph representing the values of QT and QTc dispersion (mean ± S.D.) at baseline, after epirubicin infusion ($N \pm 20$) (2 hours) and after supplementation ($N \pm 10$) or not ($N \pm 10$) with dexrazoxane (3 hours). *$P < 0.001$.

comparison with the patients who did not receive dexrazoxane therapy, who showed no significant change of QT dispersion (69.3 ± 7.6 vs. 64.2 ± 6.9 ms, ns) and QTc dispersion (72.8 ± 8.1 vs. 67.3 ± 7.2 ms, ns) (Fig. 1).

4. Discussion

In the present study we confirmed that anthracycline-based chemotherapy is associated with electrophysiological alterations such as increased QT dispersion. An interesting and novel finding of this study is that the dexrazoxane supplementation can prevent anthracycline-induced cardiotoxicity, by reducing QT dispersion.

The prolongation of QT dispersion has been linked to an increased heterogeneity of ventricular repolarization and has been shown to be associated with cardiac electrical instability and increased risk of serious cardiac arrhythmias [13, 14]. Therefore the increase of QT dispersion might not only represent a risk factor for ventricular arrhythmias in patients treated with anthracycline, but may also be a simple and inexpensive index of early myocardial impairment.

The mechanism through which anthracycline therapy determines the prolongation of QT dispersion and by which cardioxane-therapy is able to modify these electrophysiological alterations is not well known.

A possible mechanism of anthracycline-induced cardiotoxicity seems to involve the formation of free radicals leading to oxidative stress. The production of free radicals is catalyzed by an anthracycline–iron complex [15].

However, dexrazoxane is a more potent chelating agent than anthracyclines and acts by removing the iron from the complex, and therefore preventing cardiac damage [16]. In fact, the iron-overload of cardiomyocytes determines the loss of functional Na channels; enhanced Na^+ channel inactivation causes the reduction in the overshoot of cardiac action potential. These effects together with a heterogeneous pattern of iron deposition, may enhance QT dispersion. Clinical evidence of the effect of iron deposition exists in thalassemia major patients [17]. The free radical hypothesis has been supported by the finding that free radical scavengers and antioxidants such as vitamin E or probucol attenuate anthracycline-induced cardiotoxicity [18,19].

Another hypothesis on the increased QT dispersion after anthracycline-based chemotherapy is the pathological picture of anthracycline cardiotoxicity that is characterized by disruption of heart mitochondrial and sarcoplasmatic reticular membranes [20] by drug-induced free radical formation in specific myocardial compartments [21]. This effect could lead to alterations in Na–K channels activity and changes in the membrane currents, with subsequently inhomogeneity of ventricular repolarization. Several studies have shown changes in resting membrane potential and action potential amplitude [22–24].

Finally, increased QT dispersion after anthracycline-based chemotherapy may be an autonomic impairment, characterized by a reduction of parasympathetic activity [25]. Relative enhancement of vasomotor sympathetic modulation can lead to myocardial membrane properties that give rise to early afterdepolarizations and dispersion of repolarization [26]. Dexrazoxane clorhydrate may prevent autonomic dysregulation with reduced exposure of nervous autonomic cardiovascular system to epirubicin. In line, in a study with epirubicin, authors revealed an increased clearance of the anthracycline when dexrazoxane had been administered which could lead to a decreased epirubicin exposure [27].

One limitation of the present study is that the sample size was relatively small. The duration of QT intervals was measured manually. However, at the present time, studies did not show that computerized measurements are more accurate than manual measurements [28]. Recently, Tran et al. [29] recommended manual measurements as the preferred method for QT dispersion studies.

In conclusion, anthracycline-based chemotherapy causes early increase of QT interval dispersion. This effect can be attenuated by dexrazoxane treatment. Prolongation of QT dispersion may represent not only a sensitive tool in identifying the first sign of anthracycline-induced cardiotoxicity, but it may serve also in identifying patients, who are at risk of potentially fatal arrhythmic events. Whether dexrazoxane offers protection against late-onset cardiac toxicity and predicts prognosis in patients treated with anthracycline, remains to be demonstrated with further studies.

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