Introduction

A 61-year-old woman was hospitalized in our medical center because of recent syncope and palpitations. She had a history of essential hypertension, hypothyroidism and diabetes mellitus. Three years earlier, she underwent a total abdominal hysterectomy and was treated with chemotherapy owing to endometrial carcinoma. Three months before her current admission she was treated with anthracyclines owing to Hodgkin’s lymphoma. Most patients were women (n=9; 81.8%). The most prevalent triggers for Torsades de Pointes were the administration of a QT-prolonging agent (n=10; 90.9%) and hypokalemia (n=9; 81.8%). Azole derivatives were the most prevalent of the QT-prolonging agents that triggered Torsades de Pointes (n=5; 45.5%).

Although four patients suffered from anthracycline-induced left ventricular dysfunction and five other patients had only one or two questionable triggers for Torsades de Pointes, in only two of these cases the authors considered previous treatment with anthracyclines as a risk factor for Torsades de Pointes. Previous treatment with anthracycline is an underestimated risk factor for Torsades de Pointes. Possible triggers includes azole derivatives, other QT-prolonging agents and hypokalemia. Women patients are particularly at risk. Anti-Cancer Drugs 18:493–498 © 2007 Lippincott Williams & Wilkins.

Keywords: anthracycline, QT interval, Torsades de Pointes

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Anthracyclines reduce myocardial repolarization reserve and might increase the risk for Torsades de Pointes a long time after treatment. We studied all the publications concerning Torsades de Pointes in patients previously treated with anthracyclines to investigate the clinical circumstances leading to this rare life-threatening complication. Our literature search yielded nine reports of 11 patients who had developed Torsades de Pointes anywhere from weeks to years following treatment with anthracyclines. One of the patients was hospitalized in our medical center. Risk factors and triggers for Torsades de Pointes, among other clinical aspects, were analyzed in each report. Most patients (n=10; 90.9%) were previously treated with anthracyclines owing to acute leukemias: acute myelogenous leukemia (n=5), acute lymphocytic leukemia (n=3) and acute promyelocytic leukemia (n=2). One patient was previously treated with anthracyclines owing to Hodgkin’s lymphoma. Most patients were women (n=9; 81.8%).

Possible triggers includes azole derivatives, other QT-prolonging agents and hypokalemia. Women patients are particularly at risk. Anti-Cancer Drugs 18:493–498 © 2007 Lippincott Williams & Wilkins.
clinical circumstances leading to this life-threatening arrhythmia.

Material and methods

Retrieval of case reports
We performed a literature search in PubMed for all published reports, in all languages, concerning TdP in patients previously treated with anthracyclines, from 1966 until September 2006, using the following keywords: ‘TdP’, ‘Torsade de Pointes’, ‘QT interval’, ‘arrhythmia’, ‘syncope’, ‘sudden death’ and ‘anthracyclines’. The references from each report were reviewed for additional publications, as were relevant letters to the editor. We also contacted several authors for additional information and clarification. Dr Bagatell [8] and Dr Sisakova [9] were kind enough to respond.

Exclusion of case reports
The following reports were excluded: reports of sudden death with no documented TdP [10,11], reports of ventricular arrhythmias other than TdP [12–14] and reports of sudden death or arrhythmias during or directly after administration of anthracyclines [15–17].

Risk factors and triggers for Torsades de Pointes
Each case report was analyzed for the presence of risk factors or triggers for TdP: female sex [18]; cardiomyopathy and congestive heart failure [2]; hypokalemia, defined as potassium serum levels < 3.5 mmol/l [19]; hypocalcaemia, defined as calcium serum levels < 8.5 mg/dl [20]; hypomagnesemia, defined as magnesium serum levels < 1.8 mg/dl [1]; use of an agent that might trigger TdP [1]; impaired QT-prolonging agent clearance because of liver cirrhosis or renal failure [1]; HIV infection [21]; congenital long-QT syndrome, family history of long-QT syndrome, history of previous TdP and prolonged QT interval in the baseline ECG before drug initiation [22] defined as corrected QTc > 450 and calculated by the Bazzett’s formula [23].

Statistical analysis
Continuous variables, like age, Anthracyclines cumulative dose, and QTc interval, were summarized by mean, standard deviation, median, and range. Statistical analysis was performed using the SPSS (SPSS Inc., Chicago, USA) system for Windows, version 13.0.

Results
Including the patient who was hospitalized in our medical center, we reviewed nine reports of 11 patients who developed TdP starting at 15 days to over 3 years after treatment with anthracyclines [8,9,24–29]. Table 1 summarizes the clinical characteristics of the above-mentioned patients. The mean age of the reported patients was
<table>
<thead>
<tr>
<th>Number</th>
<th>Author (reference)</th>
<th>Age (years), sex (male/female)</th>
<th>Anthracyclines (cumulative dose)</th>
<th>Indication for anthracyclines</th>
<th>Timing of TdP following anthracyclines administration</th>
<th>Apparent triggers for TdP</th>
<th>Baseline QTc</th>
<th>Long QTc</th>
<th>Echo findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Otsuka et al. [28]</td>
<td>33, female</td>
<td>Daunorubicin (NA) Daunorubicin (NA)</td>
<td>AML</td>
<td>15 days</td>
<td>Pentamidine, hypokalemia</td>
<td>415</td>
<td>470</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>Tatetsu et al. [26]</td>
<td>55, female</td>
<td>Daunorubicin (NA) Daunorubicin (NA)</td>
<td>AML</td>
<td>28 days</td>
<td>Fluconazole, hypokalemia</td>
<td>375</td>
<td>528</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>Unnikrishnan et al. [27]</td>
<td>29, male</td>
<td>Idarubicin (72 mg/m²) Mitoantrone (36 mg/m²)</td>
<td>AML and relapsing AML</td>
<td>NA</td>
<td>Arsenic trioxide, hypokalemia</td>
<td>440</td>
<td>470</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>43, male</td>
<td>Idarubicin (72 mg/m²) Mitoantrone (36 mg/m²)</td>
<td>AML</td>
<td>NA</td>
<td>Arsenic trioxide</td>
<td>435</td>
<td>470</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Naito et al. [24]</td>
<td>23, female</td>
<td>Daunorubicin (720 mg/m²) Mitoantrone (24 mg/m²)</td>
<td>AML</td>
<td>3 weeks</td>
<td>Arsenic trioxide, fluconazole</td>
<td>429</td>
<td>478</td>
<td>Hypokinesis EF 51%</td>
</tr>
<tr>
<td>6</td>
<td>51, female</td>
<td>Mitoantrone (24 mg/m²)</td>
<td>AML</td>
<td>&gt;3 years</td>
<td>Arsenic trioxide, hypokalemia, hypomagnesemia</td>
<td>442</td>
<td>499</td>
<td>Hypokinesis EF 26%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Alkan et al. [29]</td>
<td>15, female</td>
<td>Anthracyclines (NA)</td>
<td>ALL</td>
<td>22 months</td>
<td>Voriconazole, ciprofloxacina, cotrimoxazole, hypokalemia</td>
<td>412</td>
<td>570</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>Kishi et al. [25]</td>
<td>16, female</td>
<td>Doxorubicin (125 mg/m²) Aclarubicin (80 mg/m²) Mitoantrone (18 mg/m²)</td>
<td>AML</td>
<td>Few months</td>
<td>Hypokalemia</td>
<td>NA</td>
<td>500</td>
<td>Hypokinesis EF 47%</td>
</tr>
<tr>
<td>9</td>
<td>Sisakove et al. [9]</td>
<td>33, female</td>
<td>Anthracyclines (NA)</td>
<td>Hodgkin’s lymphoma</td>
<td>2 months</td>
<td>Itraconazole, Terfenadine, hypokalemia</td>
<td>NA</td>
<td>500</td>
<td>EF 35%</td>
</tr>
<tr>
<td>10</td>
<td>Bagatell et al. [8]</td>
<td>16, female</td>
<td>Daunomycin (NA)</td>
<td>ALL</td>
<td>Few weeks</td>
<td>Clarithromycin, renal failure, hypokalemia, hypomagnesemia</td>
<td>388</td>
<td>566</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>Present case</td>
<td>61, female</td>
<td>Mitoantrone (36 mg/m²)</td>
<td>AML</td>
<td>3 months</td>
<td>Fluconazole, hypokalemia</td>
<td>420</td>
<td>466</td>
<td>Normal</td>
</tr>
</tbody>
</table>

ALL, acute lymphocytic leukemia; AML, acute meyeloblastic leukemia; APL, acute promyelocytic leukemia; EF, ejection fraction; NA, not applicable; QTc, corrected QT; TdP, Torsade de Pointes.
34.1 ± 16.4 years (median: 33 years, range: 15–61 years). Most of the patients were women (n = 9; 81.8%). One patient died as a result of recurrent TdP [27].

**Indications for Anthracyclines**
Most patients (n = 10; 90.9%) were previously treated with anthracyclines owing to acute leukemias: acute myelogenous leukemia (n = 5), acute lymphocytic leukemia (n = 3) and acute promyelocytic leukemia (n = 2). One patient was previously treated with anthracyclines owing to Hodgkin’s lymphoma [9].

**Anthracycline cumulative dose**
Anthracycline cumulative dose was reported in six patients and was within the recommended safe range [30] in all of these patients, except one who received a total of 720 mg/m² daunorubicin for acute promyelocytic leukemia [24].

**QTc interval**
Baseline QTc interval before administration of QT-prolonging agents was reported in eight patients and their mean QTc interval was 415 ± 23 (median: 417, range: 375–442). The QTc interval right after TdP was reported in all patients and their mean QTc interval was 497 ± 45 (median: 489, range: 440–500).

**The triggers for Torsades de Pointes**
The most prevalent triggers for TdP were the administration of QT-prolonging agents (n = 10; 90.9%) and hypokalemia (n = 9; 81.8%). Azole derivatives were the most common QT-prolonging agents to trigger TdP (n = 5; 45.5%). Arsenic trioxide use was also documented (n = 4; 36.3%). Three patients were treated with two or more QT-prolonging agents concurrently [9,24,29]. At the time of the arrhythmia, the patients had 2.3 ± 0.9 triggers for TdP and nine patients (81.8%) had ≥ 2 triggers for TdP.

**Anthracyclines-associated Torsades de Pointes**
Four patients had obvious Anthracyclines-induced left ventricular dysfunction as per echo [9,24,25]. Five more patients had only one or two questionable triggers for TdP – including the patient we presented here [26–28]. Yet, in seven of these cases, the authors (or the physicians that first treated the patient we presented) did not consider previous treatment with anthracyclines as a risk factor for TdP. Moreover, in three patients, echo was not performed or mentioned [8,26,28]. Four patients had a normal echo, but none of those authors (or the physicians that first treated the patient we presented) discussed the possibility of subclinical cardiotoxicity in their patients [27,29].

**Discussion**
Anthracyclines are the first-line therapy for many neoplastic processes. Unfortunately, anthracyclines are associated with early cardiotoxicity during the treatment or late cardiotoxicity – months–years after the treatment. Early cardiotoxicity includes supraventricular tachycardia, ventricular ectopy, myopericarditis, cardiomyopathy and death [31]. Late cardiotoxicity includes cardiomyopathy and heart failure [4–6]. Sarcoplasmic reticulum reduction, vacuole formation and necrosis in the myocardium are all histological features of anthracycline-associated cardiotoxicity. They may be explained by the following mechanisms: adenosine triphosphate depletion owing to mitochondrial dysfunction, iron–doxorubicin complex mediating free radical lipid peroxidation or a decrease in glutathione peroxidase [32].

The risk of fatal arrhythmia from weeks to years after supposedly life-saving treatment is quite troubling. Indeed, certain guidelines for cardiac monitoring and the usage of cardioprotective drugs during anthracycline administration have been established to prevent cardiotoxicity [31–34]. Withdrawal of anthracyclines from the market after years of successful clinical experience would probably harm more patients overall than it would help to prevent TdP. As our findings show that the role of previous treatment with anthracyclines in the pathophysiology of late TdP is underestimated, it is important to study the clinical circumstances by which TdP occurs following anthracycline administration.

According to Isner et al. [35], 67.1% of patients treated with anthracyclines have clinical heart failure and/or histological features of cardiotoxicity post mortem. Interestingly, 35.9% of patients with histological features of cardiotoxicity, post mortem did not have any signs or symptoms of clinical heart failure during their lifetime [35]. Although four of the patients in our study had a normal echo, subclinical cardiotoxicity was still possible, i.e. histological features of cardiotoxicity. This may explain some of our findings. It is also possible that recent administration of anthracycline itself increased the risk for TdP by increasing the dispersion of repolarization [36]. According to Milberg et al. [7], reduced repolarization reserve even in the early stages of anthracycline therapy facilitates TdP induced by hypokalemia and potassium currents blockers.

Risk factors for anthracycline-induced cardiotoxicity include female sex, cumulative dose greater than 550 mg/m², hypertension, preexisting cardiac disease, advanced age and prior mediastinal irradiation [35,37]. Although a high cumulative dose of anthracyclines is associated with increased risk for cardiotoxicity [30], some patients do not develop signs of anthracycline-induced cardiotoxicity following very high (above 5000 mg/m²) cumulative doses of anthracyclines, whereas other patients develop anthracycline-induced cardiotoxicity following very low cumulative doses (below 40 mg/m²) of anthracycline [38]. Our results are consistent with those observations: nine out of 11 patients were women.
and three out of four patients with anthracyclines-induced left ventricular dysfunction received recommended doses of anthracyclines.

**Study limitations**
The patient we described had two triggers for TdP (i.e., hypokalemia and fluconazole) and one risk factor for TdP (female sex). It is possible that anthracycline itself or subclinical cardiotoxicity following anthracycline administration increased the risk for TdP further. Although this is only a possibility, it should be highlighted as it is underestimated.

This study was based entirely on published case reports. In all of these reports, except one, the patients survived the potentially fatal arrhythmia. We believe that there are many more incidents of anthracycline-associated TdP that remain unpublished, particularly when a similar incidence involving an anthracycline had already appeared in print, when a patient had died or when a report had been rejected from publication because of apparent risk factors for TdP other than the anthracyclines treatment.

**Clinical implications and conclusions**
Patients with risk factors for anthracycline-induced cardiotoxicity or patients receiving a high cumulative dose of anthracyclines should have a baseline evaluation of cardiac function by echo or radionuclear ventriculography. Some physicians perform serial assessments of left ventricular function after every cycle of chemotherapy. Several simple aspects of the patient’s history, however, should alert physicians to a potentially increased risk for TdP. According to our findings, female patients with hematological malignancies previously treated with anthracyclines, who are currently receiving azole derivatives or other QT-prolonging agents, are at increased risk for Anthracyclines-associated TdP. These patients should be advised to promptly report any symptoms, such as palpitations or syncope. Other conditions or therapies that can cause hypokalemia, such as gastroenteritis, or the addition of a diuretic to the patient’s regimen can also increase the risk. Obtaining electrocardiograms repeatedly to detect asymptomatic prolongation of the QT interval may be warranted in such high-risk patients during administration of QT-prolonging agents; although, it is unknown whether these precautions would reduce the risk for TdP.

Finally, TdP might have been the first sign for anthracycline-induced cardiotoxicity in our patient. Hence, physicians should consider repeating the echo in patients whom have already had TdP to exclude late cardiotoxicity.

**References**


