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Case report

Paclitaxel (Taxol®)-associated junctional tachycardia

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We report the first case of junctional tachycardia in a patient treated with paclitaxel. A 60-year-old woman with advanced breast cancer received palliative chemotherapy with 22.5 mg/m^2/day paclitaxel over a 7 day continuous infusion as part of an investigational regimen. Although the patient had no previous or current history of cardiac disease, she developed severe symptomatic tachycardia, which occurred toward the end of the second and third courses. Antiarrythmic medication was prescribed and electrocardiographic records identified electric patterns of junctional tachycardia. Given both the physiopathology of arrythmic disorders and pharmacokinetics of the patient, this case report supports the hypothesis that automatic junctional rhythm after severe asymptomatic conduction block rather than direct primary toxicity on myocytes caused this toxicity.

Key words: Cardiac toxicity, continuous infusion, paclitaxel, tachycardia, taxanes.

Introduction

Paclitaxel, an anticancer agent which inhibits tubulin depolymerization,[1,2] has demonstrated antitumor activity in breast,[3] ovarian[4] and non-small-cell lung[5] cancers. Combinations with cisplatin are considered to be the new standard in ovarian cancer therapy.[4] Several schedules with paclitaxel, alone or in association with anthracyclines, have been widely used in new combination chemotherapy for advanced breast cancer and have shown specific taxane toxicity, which principally includes hypersensitivity reactions and sensitive neuropathy.[1,2] Cardiac events are rare and often non-symptomatic. They are mainly characterized by rhythm disturbances that are thought to be induced by conduction blocks.[6,7] In a few reports, those conduction blocks led to myocardial ischemias and cardiac failure.[7] Considering future combination with anthracyclines, the identification of paclitaxel-induced myocardiac toxicity warrants further clinical description. We report here the first description of a severe junctional tachycardia with clinical evidence of paclitaxel-linked causality.

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Case report

A 60-year-old Caucasian woman with advanced breast cancer was treated with a 7 day paclitaxel continuous infusion. The primary (T1, N0, M0) was diagnosed in April 1988 and treated with tumorectomy followed by 45 Gy external irradiation therapy in the left breast. She relapsed 32 months later and received several subsequent chemotherapy regimens over 60 months, including doxorubicin. The cumulative dose of doxorubicin was 450 mg/m^2, completed 50 months before paclitaxel administration. Furthermore, 1 year previous to paclitaxel administration, she received five courses of short infusion (1 h) docetaxel (at doses up to 100 mg/m^2/cycle). There was no previous history of cardiovascular disease, and both the baseline electrocardiogram and the cardiac bidimensional ultrasonography before paclitaxel were normal. This patient also had normal liver function tests before paclitaxel administration.

In October, 1995, the patient was treated with a 7 day paclitaxel continuous infusion at the dose of 22.5 mg/m^2/day, without steroid or antihistamine premedication, for a total dose of 157 mg/m^2/cycle, as part of an ongoing phase I study.[8]

The first course was completed uneventfully and pharmacokinetics were obtained as a part of the planned procedure. On the last day of the second course at the end of infusion, however, the patient immediately developed a severe 220 b.p.m. tachycardia with hypotension (90/60 mmHg) and chest pain,

without dyspnea (26/min). Pulmonary auscultation was normal and there were no other symptoms suggesting a hypersensivitity reaction. At this time, there was no clinical, electrical or radiological evidence of myocardiac failure. Electrocardiogram revealed a regular tachycardia with normal QRS complexes leading to diagnosis of junctional tachycardia (Figure 1a). Manual vagal stimulations failed and the patient received a 10 mg bolus injection of triphosphoadenosin (Striadyn®) which immediately stopped the tachycardia (Figure 1b). Cardiac enzymes and bidimensional ultrasonography were normal. The patient recovered and was discharged as planned.

The same event occurred on the fifth day of the third course of paclitaxel (Figure 1c and d) with prompt resolution after a new bolus injection of triphosphoadenosin. Clinical symptoms and electrical disorders were comparable to those experienced by the patient during the previous course of paclitaxel.

The occurrence of this event during or at the end of a 7 day paclitaxel infusion and its re-appearance during the rechallenge points us to paclitaxel as the direct cause of this effect, since there were no medications added or laboratory values changed during her treatment that might explain those symptoms. Upon evidence of disease progression, treatment was discontinued and the patient died in January 1996 without experiencing further cardiac-related problems.

Discussion

To our knowledge, this is the first report of paclitaxel-induced junctional tachycardia. While these two episodes of junctional tachycardia were not life threatening, they were symptomatic enough to require immediate treatment with triphosphoadenosin. The chronology of the events strongly suggests the responsibility of paclitaxel, since its re-introduction was associated with the same episode of tachycardia.

Including this case, a total of 14 patients (47 cycles) were treated with this regimen of paclitaxel continuous infusion in our institution,[8] pharmacokinetics were performed by high performance liquid chromatography on samples taken from all the 14 patients. In this group of patients, the serum concentration of paclitaxel ranged from 21 to 57 ng/ml[8] at the end of the 7 day infusion. The patient with junctional tachycardia was the only person who exhibited such myocardic dysfunction under treatment by paclitaxel continuous infusion. Her serum level of paclitaxel at day 7 of the first course was 37 ng/ml. Therefore we assumed that the episode of junctional tachycardia was not due to an increase in serum concentration of paclitaxel, since her serum level was within the range of serum concentration values for the other patients who did not present any cardiac dysfunction. Moreover, the accumulation of a toxic metabolite was unlikely since the total dose of paclitaxel received

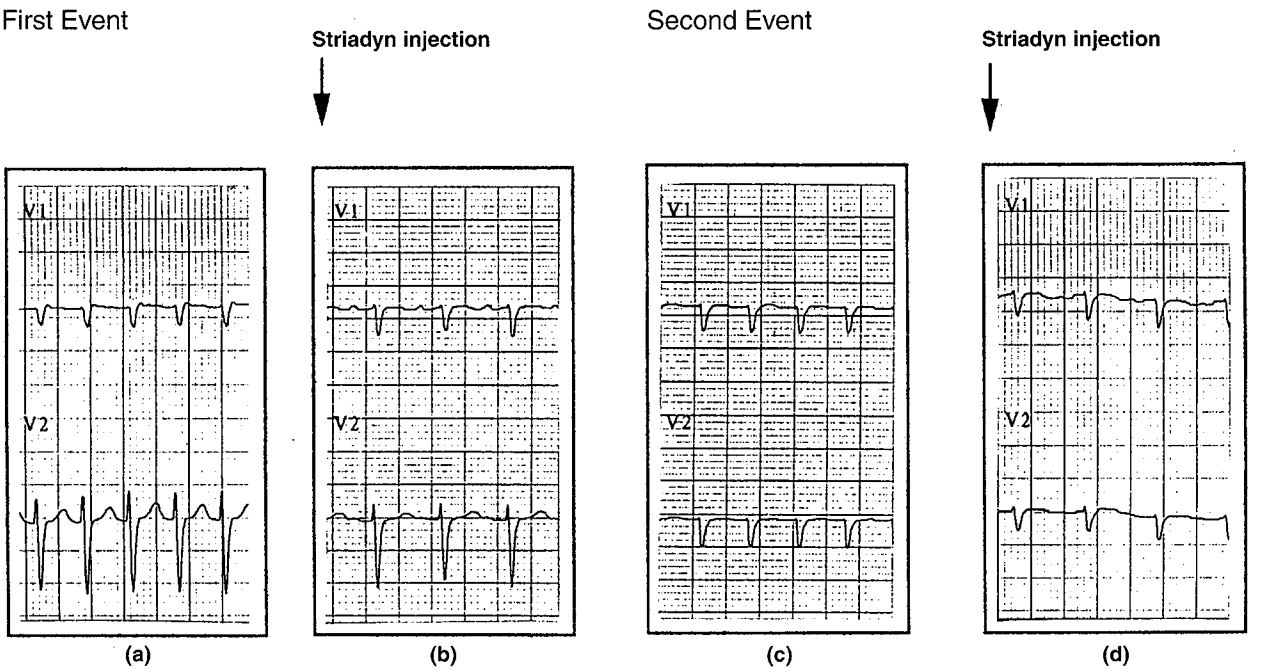

Figure 1. Junctional tachycardia in a patient treated with continuous infusion paclitaxel. Two episodes of tachycardia were observed (a and c) and were reversible after triphosphoadenosin injection (b and d).

during each course was less than the recommended dose range (135 or 175 mg/m^2) and was given in the absence of liver dysfunction, which is known to affect taxane metabolism.

In the excellent review by Arbuck *et al.*,[7] which lists all known paclitaxel-associated cardiac dysfunctions, no junctional tachycardia is reported. Prospective cardiac monitoring reveals the frequent occurrence of asymptomatic cardiac arrhythmias, including sinusal bradycardias and conduction blocks (either auriculo-ventricular or partial left bundle blocks).[7,9] Generally in patients with cardiovascular risk factors, more severe complications (such as auricular or ventricular tachycardias, acute myocardial ischemias and sudden deaths)[6,7] have been described. Moreover, the association of paclitaxel with doxorubicin has shown to be particularly cardiotoxic, primarily to myocardial function itself.[10]

The underlying mechanisms of paclitaxel cardiotoxicity are partially known. The excipient Cremophor has been shown to induce cardiotoxicity and its role in paclitaxel-associated cardiac events has been suggested.[7] However, the Cremophor-related toxicity consisted of myocardic dysfunctions and cardiac arrhythmia has never been reported.

An *in vitro* model utilizing primary cardiac cultures from Sprague-Dawley newborn rats has suggested that paclitaxel cardiotoxicity may be mediated through an alteration of the cardiac cell microtubules. However, these rhythm disturbances are correlated with paclitaxel concentrations above 100 ng/ml.[11] Since in our case report the serum concentration was lower than those associated with cardiotoxicity *in vitro*, we may assume that other mechanisms that alter microtubules are involved in paclitaxel-induced junctional tachycardia.

Conclusion

In summary, while this observation is probably a sporadic incident within the spectrum of possible paclitaxel-related toxicity, the specific symptoms linked to conduction defects required an urgent diagnosis and immediate therapy. Moreover, this report may complement an overall explanation for different cardiac rhythm disturbances that have been reported in the literature. We propose that the observed ventricular and junctional (described herein) tachycardias are not due to primary cardiac toxicity on myocytes but may represent the consequences of conduction blocks, which are fairly prevalent and usually subclinical under treatment with paclitaxel.[7] Junctional tachycardias result frequently as an escape mechanism of intra-nodal re-entry due to the presence of an accessory pathway. Thus, the present episode of tachycardia may reflect automatic junctional rhythm after severe asymptomatic sinusal or auriculo-ventricular block.

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