Eur J Med Res (2005) 10: 498-501 © I. Holzapfel Publishers 2005

Case Report

Symptoms and Signs of an Acute Myocardial Ischemia Caused by Chemotherapy with Paclitaxel (Taxol) in a Patient with Metastatic Ovarian Carcinoma

C. Schrader[1], C. Keussen[2], B. Bewig[3], A. von Freier[3], M. Lins[3]

[1]II. Department of Internal Medicine, [2]Department of Gynecology, [3]Department of Cardiology,
University Hospital of Schleswig-Holstein, Kiel, Germany

Abstract:
Introduction: Paclitaxel (Taxol) is an anticancer agent used for the treatment of breast and ovarian cancer. The major side effects are bone marrow suppression, alopecia, polyneuropathy and cardiac toxicity like bradycardia, myocardial infarction, congestive heart failure and cardiac death.
Setting: Intensive care unit (ICU) of a university hospital.
Patient: We report on a 58-years-old woman with a metastatic ovarian carcinoma who had chest pain, nausea and collapse during their first Taxol infusion. The infusion was stopped and the patient was submitted to the intensive care unit (ICU) to exclude an acute coronary syndrome.
Results: The electrocardiography (ECG) showed a third-degree heart block and ST elevation in II, III and avF. In the initial and in the control laboratory investigation values of cardiac enzymes (creatininkinase and Troponine T) remained normal. The control ECG after 30 minutes turned back to normal. After one day the patient was submitted back to a normal ward.
Conclusion: Symptomatic bradyarrhythmia and clinical sign of an myocardial infarction are rare but important cardiac side effects in patients treated with Taxol. Those patients should be under intensive care unit until patients conditions improve and acute myocardial ischemia has been excluded.

Key words: paclitaxel, taxol, heart block, angina pectoris, bradyarrhythmia, chemotherapy

Introduction

Paclitaxel (Taxol) was discovered in 1963 in an extract from the bark of the evergreen *Taxus brevifolia* in the forest of the Pacific Northwest. Preclinical studies showed that it has cytotoxic activity against many tumors [1]. Taxol is currently one of the most commonly used antineoplastic agents in standard oncology practice. It has been reported to be an effective chemotherapeutic drug in treating metastatic ovarian and breast carcinoma [2].

The mechanisms of Taxol as an anticancer agent are well known. It polymerizes microtubuli, that have function in the formation of the mitotic spindle during cell division. By this interaction, the normal microtubuli dynamic is disruted. Mitosis and cell turnover of tumor cells are decreased [3, 4]. Additionally, Taxol induces the expression of tumor necrosis factor a (TNF α) that plays an important role in cell death, because TNF could induce apoptosis [2].

Microtubuli are also involved in many vital functions like signal transmission and intracellular transport. The major side effects of Taxol are bone marrow suppression, hypersensitivity reactions, alopecia and neurotoxicity [2]. Other side effects are cardiac toxicity with bradycardia, myocardial infarction, congestive heart failure and cardiac death. Transient asymptomatic bradycardia has been reported very frequently in about 30% of patients, wheras symptomatic third-degree heart blocks are rare [5].

We present a patient with a metastatic ovarian carcinoma who developed chest pain, vomiting and a symptomatic bradyarrhythmia caused by chemotherapy with Taxol. Clinical symptoms and the initial ECG-findings were mimicking an acute myocardial ischemia. This rare but important side effect has to be considered in treating patients with Taxol.

Case Report

A 58-years-old woman was submitted to intensive care unit of our hospital with suspect of a myocardial ischemia. There was no history of a coronary heart disease and diabetes. The patient is a non-smoker and was healthy for the last years. Besides she was hypothyreotic.

Now the woman had a metastatic ovarian carcinoma (FIGO IIIC) that had been diagnosed four weeks ago in the Department of Gynecology. A combinated chemotherapy with Carboplatin (370mg absolute) and Taxol (256mg absolute) was given for the first time. 20 minutes after start of the Taxol infusion, the patient collapsed and developed symptoms of chest pain and nausea. The infusion was stopped and the patient received 250mg prednisone intravenously, assuming that the patient had a hypersensitivity reaction. When the patient did not recover an ECG was performed. The initial ECG (Fig. 1) showed a third-degree heart block and ST elevation in II, III and avF.

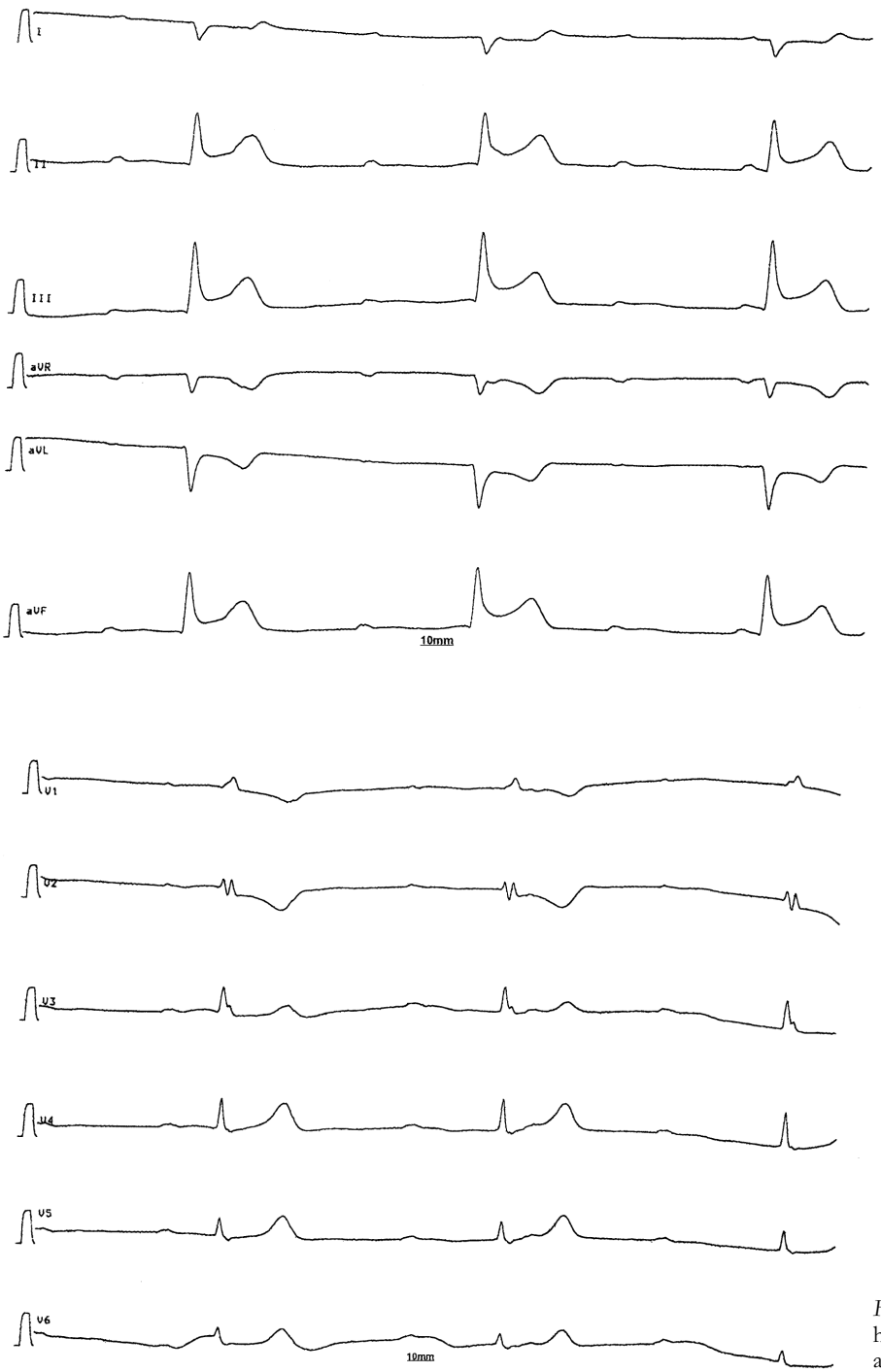

Fig. 1. Initial ECG with a third-degree heart block and ST elevation in II, III and avF (heart rate: 35 bpm).

The heart rate decreased to 35 bpm and the blood pressure droped down to 90/50 mmHg. The patient received heparin intravenously and was transfered to our department. The initial and control laboratory findings did not show elevation of the cardiac enzymes creatininkinase and Troponin T. Transthoracic echocardiography showed normal left ventricular function. The control ECG (Fig. 2) done 30 minutes later was normofrequent with 99 bpm without a heart block.

The patients conditions improved rapidly with increasing heart rate and blood pressure as well as chest pain and nausea disappeared. After one day monitoring, the patient went back to a normal ward.

Discussion

Breast cancer is one of the mostly malignant diseases that occur in women. In advanced stages of the disease, systemic chemotherapy is the treatment of choice. Since about twenty years Taxol plays an important role as a first line treatment in this disease [2]. Therefore it is one of the frequently used chemotherapeutic agents. There is evidence that other malignant diseases, e.g. ovarian cancer, can be treated with this drug as well [6, 7]. The mechanism of Taxol is well investigated. It polymerizes microtubuli that function in cells as spindle cords during mitosis in cell division.

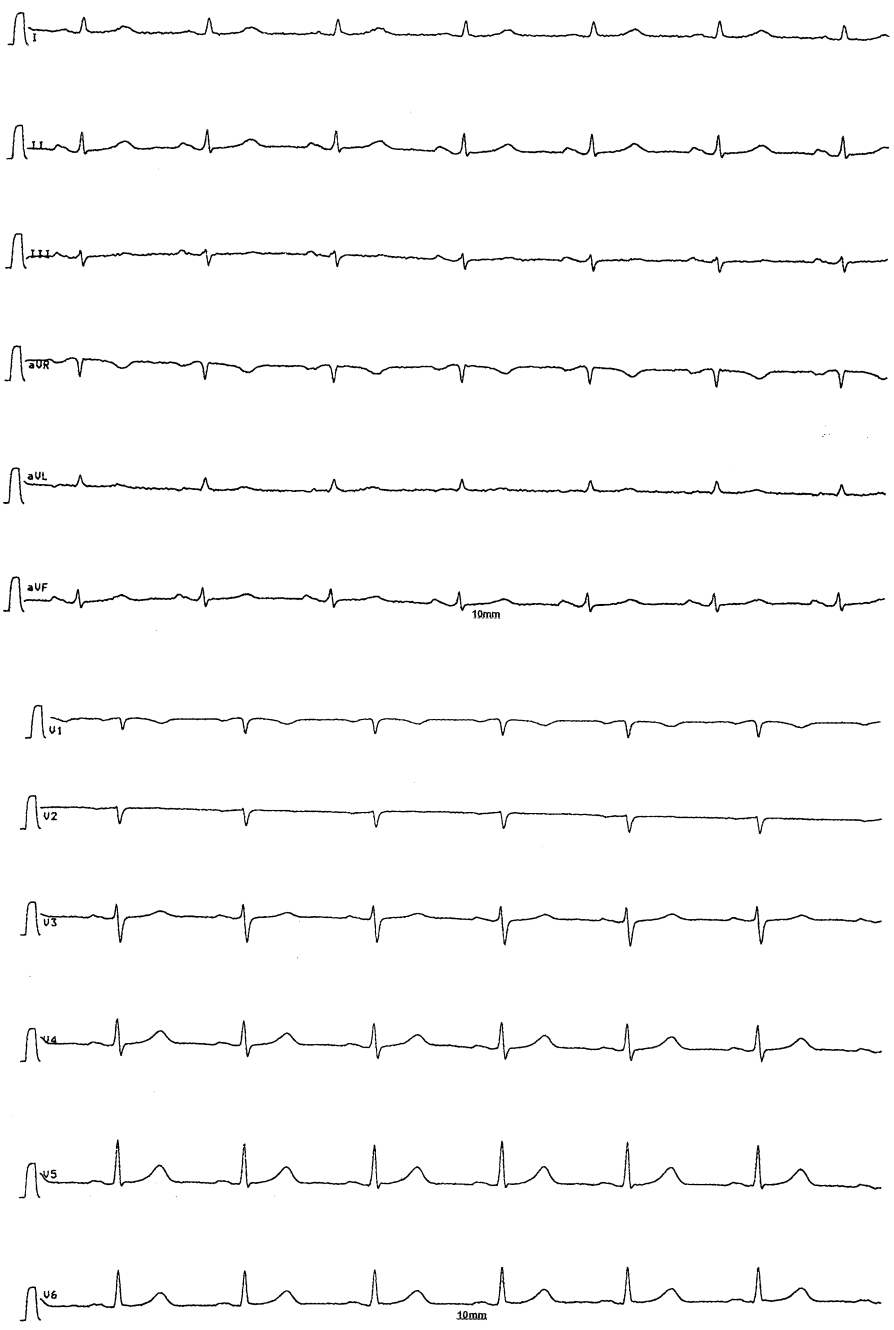

Fig. 2. The control ECG 30 minutes after stop of Taxol infusion: normal sinus rhythm (99 bpm), no ST-segment elevation.

The main function of Taxol in breast cancer cells is an interaction with inhibition of these spindles that causes cell death of the tumor cells. The interaction of Taxol with cells that have a high turnover also leads to hematopoetic cytopenia (anemia, granulocytopenia and thrombocytopenia). Other major side effects might be explained by the fact that also nervous and muscle cells have microtubuli. In nervous cells the interaction may cause polyneuropathy.

In isolated myocytes microtubuli are located around the nucleus and extramyofibrillar. Microtubuli have a close association with mitochondria, myofilament bundles and the sarcoplasmic reticulum and regulates Calcium handling in myocytes [8]. The polymerization of the microtubuli by Taxol causes a reduction of the Calcium transient in the sarcoplasmic reticulum. This reduced release of Calcium from the sarcoplasmic reticulum is a reason for the negative inotropic effect of Taxol [9]. This interaction can cause brady- and tachyarrhythmia and even coronary spasm with myocardial ischemia [6]. Cardiac toxicity of Taxol has been that extended that a cardiac monitoring was recommended in several studies [7]. The cardiac montitoring is not necessary routinely, but should be done in patient with known atrioventricular conduction defects and with ventricular dysfunction [2].

We report on a woman who had clinical sign of myocardial ischemia (symptomatic bradycardia, angina pectoris and nausea) after Taxol infusion. Because ECG-changes with ST-elevation were documented at

the inferior leads our patient might have had a coronary spasm of the right coronary artery that causes symptomatic angina pectoris and bradycardia due to complete atrio-ventricular block.

Our patient was normofrequent without any symptoms one hour after the end of Taxol infusion. The enzymes were not elevated and a myocardial ischemia could be excluded.

This report demonstrates an important cardiac side effect of Taxol, one of the frequently used chemotherapeutic agents. Beside many other side effects, Taxol can cause cardiac symptoms and a myocardial infarction has to be excluded in these patients. Patients with cardiac risk factors should be treated with Taxol under cardiac montitoring.

REFERENCES

1. Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT (1971) Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. J Am Chem Soc 93:2325-27.
2. Rowinsky EK, Donehower RC (1995) Paclitaxel (taxol). N Engl J Med 332:1004-14.
3. Alloatti G, Penna C, Gallo MP, Levi RC, Bombardelli E, Appendino G (1998) Differential effects of paclitaxel and derivatives on guinea pig isolated heart and papillary muscle. J Pharmacol Exp Ther 284:561-67.
4. Schiff PB, Fant J, Horwitz SB (1979) Promotion of microtubule assembly in vitro by taxol. Nature 277:665-67.
5. Rowinsky EK, McGuire WP, Guarnieri T, Fisherman JS, Christian MC, Donehower RC (1991) Cardiac disturbances during the administration of taxol. J Clin Oncol 9:1704-12.
6. McGuire WP, Rowinsky EK, Rosenshein NB, Grumbine FC, Ettinger DS, Armstrong DK, Donehower RC (1989) Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Ann Intern Med 111:273-79.
7. Thigpen JT, Blessing JA, Ball H, Hummel SJ, Barrett RJ (1994) Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study. J Clin Oncol 12:1748-53.
8. Goldstein MA, Entman ML (1979) Microtubules in mammalian heart muscle. J Cell Biol 80:183-95.
9. Howarth FC, Calaghan SC, Boyett MR, White E (1999) Effect of the microtubule polymerizing agent taxol on contraction, Ca2+ transient and L-type Ca2+ current in rat ventricular myocytes. J Physiol 516:409-19.

Received: June 20, 2005 / Accepted: September 28, 2005

Address for correspondence:
Carsten Schrader, MD
II. Department of Internal Medicine
University Hospital of Schleswig-Holstein, Kiel
Chemnitzstr.33
D-24116 Kiel, Germany
Tel.: +49/431/16975220
Fax : +49/431/16971202
e-mail: c.schrader@med2.uni-kiel.de