CARDIOTOXICITIES OF PACLITAXEL IN AFRICAN AMERICANS

Padma Kamineni, MD; Kalpana Prakasa, MD; Syed P. Hasan, MD, FABHP; Ravi Akula, MD; and Fitzroy Dawkins, MD

Washington, DC

Purpose: To assess the cardiac disturbances in African-American patients treated with paclitaxel.

Patients and Methods: One-hundred-nineteen African-American patients received paclitaxel for various cancers at Howard University Hospital during the years 1993–2001. Medical records of 100 patients were available for review. Sixty-seven percent were women and 33% were men. Ages ranged between 26–85 years (mean age 51 years). Medical records were reviewed for demographics, types of cancer, dosage and frequency of paclitaxel and other chemotherapeutic agents, events during paclitaxel infusion, initial and subsequent EKGs, and hospital admissions. We used the Chi-square test to compare EKG changes in patients with and without cardiac risk factors.

Results: Ninety patients received paclitaxel as second-line chemotherapy, and 10 patients were treated with paclitaxel as a single agent. Dosage of paclitaxel ranged from 75–200 mg/square meter and was administered every 1–3 weeks. The electrocardiogram readings revealed the following cardiac events: 26% sinus tachycardia, 13% non-specific T-wave changes, 6% myocardial infarction, 4% prolonged QT interval, 4% left-bundle branch block, 3% right-bundle branch block, 3% sinus bradycardia, 2% premature atrial contractions, 2% premature ventricular contractions, 2% atrial flutter, and 1% atrial fibrillation. Eighty percent of the patients had risk factors for coronary artery disease. These cardiac disturbances were observed from day one to a maximum of eight years after receiving the chemotherapy and were independent of dosage of paclitaxel.

Sixty percent of our study population had underlying co-morbid conditions, such as dehydration, anemia, sepsis, and hypoxia. The EKG changes observed in patients with underlying cardiac risk factors were statistically significant ($p<0.0001$).

Conclusion: Paclitaxel was not associated with significant symptomatic cardiac disturbances during infusion in our study population. Caution should be exercised in patients with underlying cardiac disease and risk factors for coronary artery disease. However more prospective studies with closer follow-up during paclitaxel infusion are needed to assess its cardiotoxicities. (*J Natl Med Assoc.* 2003;95:977–981.)

Key words: paclitaxel ♦ cardiotoxicities ♦ arrhythmia

INTRODUCTION

Paclitaxel is a natural product with antineoplastic activity originally isolated from the bark of the Pacific yew tree, Taxus brevifolia. It is the prototype of a novel class of antimicrotubule agent that induces tubulin polymerization. Its other mechanisms of action include: stimulating production of tumor necrosis factor (TNF) alpha in macrophages; down-regulating TNF-alpha receptors; increasing mRNA levels for TNF-alpha, interleukin-1, and interleukin-6; and inducing tyrosine phosphorylation of several proteins[1]. It is widely used in the treatments of breast, ovarian, and lung cancers; Kaposi's sarcoma; and other solid tumors. Paclitaxel-coated coronary stents may be indicated to reduce the restenosis rate[2]. Evidence linking paclitaxel to cardiotoxicities arose from early phase-1 trials, in which continuous cardiac monitoring was performed because of major

 Send correspondence and reprint requests for *J Natl Med Assoc.* 2003;95:977–981 to: Syed Hasan, MD, FABHP, Center for Sickle Cell Disease, 2121 Georgia Ave NW, Washington, DC 20059; phone: (202) 865-6100; fax: (425) 963-8879; e-mail: syedphasan@hotmail.com

Table 1. Characteristics of the Study Population	
Mean age	51 years
Sex	67% women and 33% men
Presence of cardiac risk factors	80%
Post-menopausal women	42%

hypersensitivity reactions. Various cardiac manifestations have been reported in the literature, ranging from asymptomatic tachy and brady arrhythmias to fatal myocardial infarctions[3]. African Americans have higher incidence and prevalence of cardiovascular diseases[4]. The purpose of this study is to retrospectively assess the cardiotoxicities of paclitaxel in African Americans.

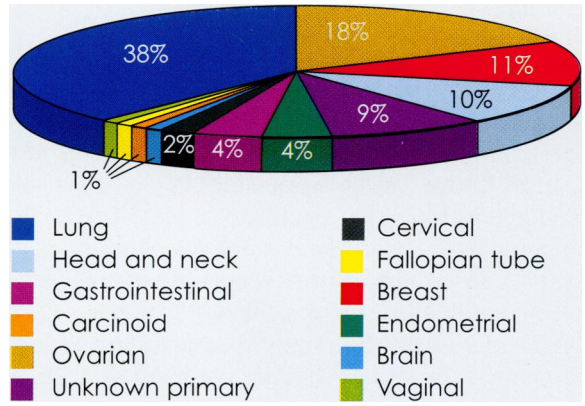
PATIENTS AND METHODS

One-hundred-nineteen African-American patients received paclitaxel for various cancers at Howard University Hospital during the years 1993–2001. Institutional review board approval was obtained. Medical records of 100 patients were available for review. Sixty-seven percent were women, and 33% were men. Ages ranged between 26–85 years. The mean age of the study population was 51 years. Eighty percent of patients had risk factors for coronary artery disease. Forty-two were post-menopausal women (Table 1). Medical records were reviewed for demographics, types of cancer, dosage and frequency of paclitaxel and other chemotherapeutic agents, events during paclitaxel infusion, initial and subsequent EKGs, and hospital admissions. We used the Chi-square test to compare EKG changes in patients with and without cardiac risk factors.

RESULTS

Ninety patients received paclitaxel as second-line chemotherapy, and 10 patients were treated with paclitaxel as a single agent. Thirty-eight lung, 18 ovarian, 11 breast, 10 head and neck, four gastrointestinal, four endometrial, two cervical, one fallopian tube, one vaginal, one carcinoid, one brain and nine unknown primary cancers were treated with paclitaxel (Figure 1). Dosage of paclitaxel ranged from 75–200 mg/square meter, administered every 1–3 weeks. The available EKGs, which were obtained for various reasons from a one-day to eight-year follow-up period, have been reviewed. Our study revealed the following cardiac events: 26% sinus tachycardia (sinus tachy), 13% non-specific T-wave changes (NS-T wave changes), 6% myocardial infarction (MI), 4% prolonged QT interval, 4% left-bundle branch block (LBBB), 3% right-bundle branch block (RBBB), 3% sinus bradycardia (sinus brady), 2% premature atrial contractions (PAC), 2% premature ventricular contractions (PVC), 2% atrial flutter, and 1% atrial fibrillation (A-fib) (Figure 2).

Figure 1. Types of Cancer Patients (%) Treated With Paclitaxel



Sinus tachycardia was the most common arrhythmia (26%) observed in our study—in contrast to other studies reporting sinus bradycardia in 29–30% of the cases[6,7]. Increased frequency of sinus tachycardia in our patients could be explained by co-morbid conditions like anemia, hypoxia, sepsis, and dehydration. Non-specific T-wave changes resolved within a few days. Six patients were noted to have uncomplicated myocardial infarction (Table 3), and four of them had a history of old myocardial infarction. The remaining two myocardial infarctions occurred during the follow-up period: one at three months and the other at one year. Eighty percent of our patients had risk factors for coronary artery disease. None of the patients had significant symptomatic cardiac disturbances during chemotherapy infusion.

None of our patients who had arrhythmias were found to have electrolyte imbalances or thyroid dysfunction. Sixty percent of the patients with these arrhythmias had underlying co-morbid conditions, such as dehydration, anemia, sepsis, and hypoxia. One patient became hypotensive during infusion, one experienced abdominal pain, two complained of dizziness, and two developed chest pain. EKGs obtained during these symptoms were normal. The follow-up period ranged from one day to a maximum of eight years after paclitaxel infusion.

Table 2. EKG's Changes in the Patients With and Without Cardiac Risk Factors

Cardiac Risk Factors	Normal EKG	Abnormal EKG	Total # of patients
Absent	17	3	20
Present	17	63	80

Fourteen patients died during the follow up secondary to advanced cancer. None of them died during or immediately following paclitaxel infusion. We also compared the EKG changes in the patients who have positive cardiac risk factors versus the patients who have no cardiac risk factors. Twenty patients—17 of which had normal EKG findings, and three of which had sinus tachycardia—had no cardiac risk factors. One patient with sinus tachycardia had anemia as a co-morbid condition (Table 2). When using the Chi-square test to compare the EKG changes in patients with and without cardiac risk factors, we found statistically significant ($p<0.0001$) EKG changes in patients with cardiac risk factors.

DISCUSSION

The cardiotoxic effects of paclitaxel, which include sinus bradycardia, sinus tachycardia, atrial fibrillation, atrio-ventricular, and bundle branch blocks, usually manifest as arrhythmia. Cardiotoxicities manifested during infusion of the drug are usually asymptomatic, mild, and reversible[3,5-7]. Rowinsky et al.[6], in 1991, reviewed adverse cardiac events during administration of paclitaxel. They noted asymptomatic sinus bradycardia in up to 30% of patients, and other arrhythmias—including AV conduction block, left-bundle branch block, ventricular premature contractions, ventricular tachycardia, and ischemic manifestations—in 5% of patients[3].

McGuire et al.[7] noted asymptomatic bradycardia during infusion in 29% of their study population. It was the most common arrhythmia. Rarely serious arrhythmias requiring pacemaker have been reported[7]. However, sinus tachycardia was the most common arrhythmia noted in our study which could be attributed to underlying co-morbid conditions, such as dehydration, anemia, sepsis, and hypoxia. Continuous cardiac monitoring during chemotherapy infusion was not performed in our study population. This might have contributed to lower incidence of bradycardia in our patients, as arrhythmias are often transient.

Chang et al. reported two cases of fatal myocardial infarction[8]. A fatal case of congestive heart failure after paclitaxel infusion was reported by Jekunen et al. in 1994[9]. The ultra structural abnormalities found in the myocardium of patients who died after paclitaxel administration, however, are not pathognomic of paclitaxel and have been described after treatment with anthracyclines[10-13]. Fragmentation, loss of myofibrils, and dilatation of the sarcoplasmic reticulum and T-tubule system with or without myelinoid figures in cardiac muscles have been described in patients treated with paclitaxel, as well as anthracyclines[14].

In our study, it is clear that these changes were a result of underlying cardiac risk factors and co-morbid conditions. One patient developed hypotension during paclitaxel infusion. He responded to fluid resuscitation and subsequently received paclitaxel without cardiac complications. One complained about abdominal pain during paclitaxel infusion. It is probable that mesenteric vessel ischemia might have contributed to the abdominal pain, but it was transient and resolved without any intervention. Dizziness and chest pain were each experienced by two patients during chemotherapy infusion and found to be transient in duration and did not require

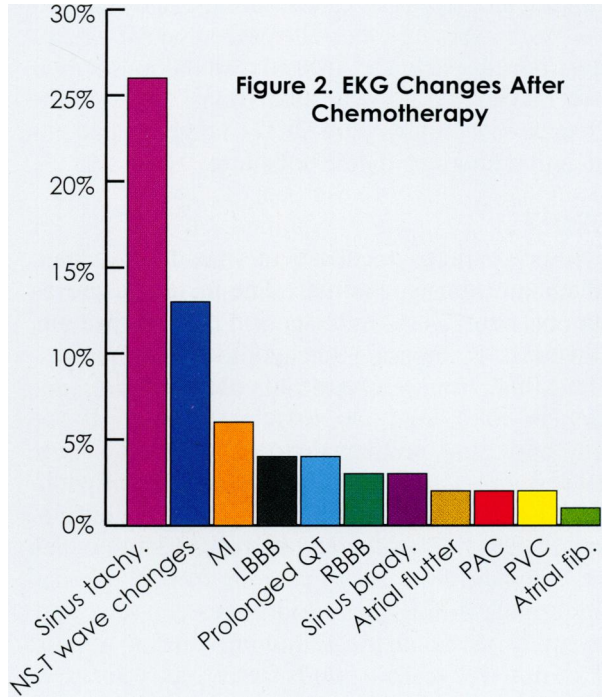


Table 3. Characteristics of Myocardial Infarction Patients

#	Age	Sex	Risk Factors	Type of Cancer	Timing of MI
1	67	F	Hypertension, H/O* MI, Post-menopausal	Colon cancer	Prior to paclitaxel infusion
2	80	F	Smoking, H/O* MI Post-menopausal	Lung cancer	Prior to paclitaxel infusion
3	65	F	CAD,+ Hypertension, Smoking	Breast cancer	One year after paclitaxel infusion
4	60	F	Smoking, Post-menopausal	Laryngeal cancer Endometrial cancer	Three months after paclitaxel infusion
5	75	F	Hypertension, H/O* MI, Post-menopausal	Ovarian cancer	Prior to paclitaxel infusion
6	70	M	Smoking, H/O* MI, S/P,** CABG,++ Hypertension	Lung cancer, oropharyngeal cancer, prostate cancer	Prior to paclitaxel infusion

* History of
\+ Coronary Artery Disease
** Status Post
\++ Coronary Artery Bypass Graft

discontinuation of chemotherapy or any intervention. No arrhythmia or myocardial ischemia was associated with these symptoms.

In our study 50% of the cardiac arrhythmias were noted in patients with lung cancer. Thirty-eight patients had lung cancer. They were ex-smokers and were more likely to be hypoxic during these cardiac events. Thirty-one of 100 patients had echocardiographic assessment during follow-up period. Six (19.4%) of them had pulmonary hypertension. Hypoxia and pulmonary hypertension could explain cardiac arrhythmias in our patient population. Though all of our patients didn't have echocardiographic assessment, prevalence of pulmonary hypertension could be higher in our study population. Cherifi et al. reported acute pulmonary hypertension following paclitaxel in a patient with AIDS-related primary effusion lymphoma[15]. The increased prevalence of pulmonary hypertension in our patients could be the result of chronic hypoxia and/or anemia.

Paclitaxel has been shown to enhance the metabolism of doxorubicin to toxic species in human myocardium[16]. A study on doxorubicin conducted at our institution showed that African Americans had a higher rate than caucasians (10/399) of cardiotoxicity after doxorubicin therapy (7/100). This rate was statistically significant at $p<0.027$[17]. Cardiotoxicity in their study was defined as congestive heart failure or left ventricular ejection fraction less than 45%. None of our patients received paclitaxel and doxorubicin during the same chemotherapy cycle. Doxorubicin was given as first line chemotherapy and paclitaxel was given as second-line chemotherapy in our study population.

Drisko et al. showed beneficial effects of coenzyme Q-10 with other antioxidants in two patients with ovarian cancer who received paclitaxel and carboplatinum as first line of chemotherapy (18). However, randomized, controlled trials using coenzyme Q-10 are underway. None of our patients received coenzyme Q-10.

CONCLUSION

Paclitaxel was not associated with significant symptomatic cardiac disturbances during infusion in our study population. The significant electrocardiographic changes were observed in patients with risk factors for coronary artery disease and co-morbid conditions. However, in their study population, McGuire et al.[7] reported 29% asymptomatic bradycardia during paclitaxel infusion. Oncologists should therefore be alert to potential cardiac complications of paclitaxel in patients with co-morbid cardiac diseases. Continuous cardiac monitoring should be considered in this group of patients. However, more prospective studies with closer follow-up during paclitaxel infusion are needed to assess the real incidence of drug-induced cardiotoxicities.

ACKNOWLEDGEMENTS

We acknowledge Dr. John Kwagyan for his great help in analyzing the statistical part of our study, and Srinivasulu Rayala and Balaji Prakash Rao for their assistance in incorporating the computer graphics and text.

REFERENCES

1. Laher S, Karp SJ. Acute myocardial infarction following paclitaxel administration for ovarian carcinoma. *Clin Oncol.* 1997; 9:124-126.

2. Honda Y, Grube E, De La Fuente LM, Yock PG, Stertzer SH, Fitzgerald PJ. Newer intracoronary stents. *Circulation.* 2001;104:380-383.

3. Rowinsky EK, McGuire WP, Guarnieri T, Fisherman JS, Christian MC, Donehower RC. Cardiac disturbances during the administration of paclitaxel. *J Clin Oncol.* 1991;9:1704-1712.

4. Davis SK, Liu Y, Gibbons GH. Disparities in trends of hospitalization for potentially preventable chronic conditions among African Americans during the 1990s: implications and benchmarks. *Am J Public Health* 2003;93:447-455.

5. Anonymous. Paclitaxel. *Lancet.* 1992;339:1447-1448.

6. Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel. *Semin Oncol.* 1993;20 (suppl 3):1-15.

7. McGuire WP, Rowinsky EK, Rosenshein NB, et al. Paclitaxel: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. *Ann Intern Med.* 1989:111:273-279

8. Chang AY, Kim K, Glick J, Anderson T, Karp D, Johnson D. Phase-2 study of paclitaxel, merbarone, and piroxantrone in stage-4 non-small-cell lung cancer: the Eastern Cooperative Oncology Group results. *J Natl Cancer Inst.* 1993;85:388-394.

9. Jekunen A, Heikkila P, Maiche, Pyhonen S. Paclitaxel-induced myocardial damage detected by electron microscopy. *Lancet.* 1994:343:727-728.

10. Billingham ME. Role of endomyocardial biopsy in diagnosis and treatment of heart disease. In Silver MD, ed. Cardiovascular Pathology: 2nd ed. New York, NY; Churchill Livingstone Inc; 1991:1472-1475.

11. Billingham ME, Bristow MR, Glatstein E, Mason JW, Masek MA, Daniel JR. Adriamycin cardiotoxicity; endomyocardial biopsy evidence of enhancement by radiation. *Am J Surg Pathol.* 1977;1:17-23.

12. Buja LM, Ferrans VJ, Mayer RJ, Roberts WC, Henderson ES. Cardiac ultrastructural changes induced by daunorubicin therapy. *Cancer.* 1973;32:771-788.

13. Mackay B, Ewer MS, Carrasco CH, Benjamin RS. Assessment of anthracycline cardiomyopathy by endomyocardial biopsy. *Ultrastruct Pathol.* 1994;18:203-211.

14. Shek TWH, Luk ISC, Ma L, Cheung KL. Paclitaxel-induced cardiotoxicity. *Arch Pathol Med.* 1996;120:89-91.

15. Cherifi S, Hermans P, Wit SD, Cantinieaux B, Clumeck N. Acute pulmonary hypertension following paclitaxel in a patient with AIDS-related primary effusion lymphoma. *Clin Micro & Infect.* 2001;7:277.

16. Minotti G, Saponiero A, Licata S, Menna P, Calafiore AM, Teodori G, Gianni L. Paclitaxel and docetaxel enhance the metabolism of doxorubicin to toxic species in human myocardium. *Clin Cancer Res.* 2001;7:1511-1515.

17. Dinh K, Hasan S. *South Med J*, Suppl. 2002;95:S5.

18. Drisko JA, Chapman J, Hunter VJ. The use of antioxidants with first-line chemotherapy in two cases of ovarian cancer. *J Am Coll Nutr.* 2003;22:118-123.