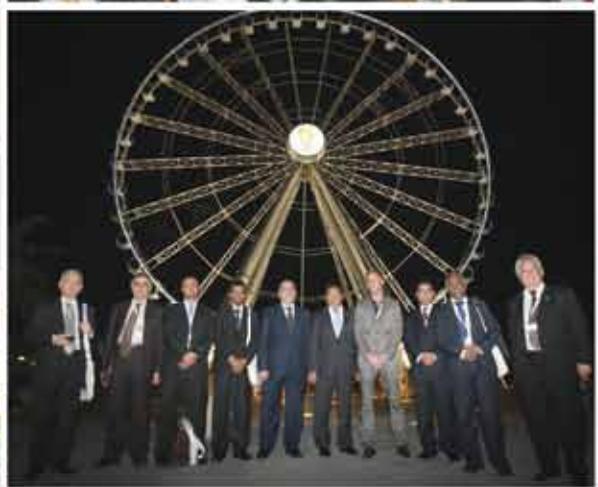


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TABLE OF CONTENTS

Original Studies

- Mutations in EGFR Signal Pathway in Correlation with Response to Treatment of Head and Neck Cancers** 07
J. Neuwirthová, S. Pavel, J. Rottenberg, R. Kostřica, M. Zdeněk, M. Hajdúch, J. Drábek, J. Srovnal, J. Berkovcová
- Comparison of IMRT and Rapidarc treatment plans using AAPM task group test suites** 11
S. Sathiyar, M. Ravikumar, A.L. Boyer, J. Shoales
- Clinical significance of hTERT and C-Myc genes amplification in a group of Egyptian patients with cancer cervix** 18
M.M. Eid, H.M. Nossair, M.T. Ismael, G. Amira, M.M. Hosney, R. Abdul Rahman
- Disease profile and treatment results of anal canal SCC: Experience from AIIMS, New Delhi** 27
R. Hadi, BK Mohanti, S. Pathy, NK Shukla, SVS Deo, A. Sharma, V. Raina, GK Rath
- Prediction of Anthracycline Induced Cardiotoxicity: Study of thirty-one Iraqi adult patients** 33
AMJ Al-Mudhafar, AAS Ali
- Early Gastrointestinal Complications of Stem Cell Transplant - Results of Prospective Study at IRCH, AIIMS, India** 40
G.M. Bhat
- Medullary Carcinoma of the Breast: Ten Year Clinical Experience of the Kuwait Cancer Control Centre** 45
S.M. Samir, M.S. Fayaz, A. Elbasmy, M.M. Motawy, S.Abuzallouf, T. George, M. Abdelhady, A. Bedair
- Respiratory gated simultaneous integrated boost-intensity modulated radiotherapy (SIB-IMRT) after breast conservative surgery for carcinoma of the breast: The Salmaniya Medical complex experience** 53
D. Majumdar, S.S. Mohammed, M.A. Naseer, J. Jacob, R. Mohan, S.B. Ebenezer, B. Al-Najar, S. Al-Janahi, V. Ramanathan, S.A. Sabt, R.S. Patnaik, A. Hassan

Case Reports

- Temporary Asymptomatic Sinus Bradycardia with Carboplatin, Paclitaxel and Bevacizumab: Under-reported in Clinical Trials and under-disclosed in practice** 60
J. Zekri
- Verruciform xanthoma of the penis in a young male masquerading as squamous cell carcinoma: Case Report** 65
M. Kukreja, M. Kamal, R. Ray, AASR Mannan
- Acute respiratory distress syndrome in poor prognostic germ cell tumor with multiple lung metastases: A case report** 69
M.A. Naseer, S.S. Mohammed, S.K. Das Majumdar, R. Patnaik, H.M.N. Al Tublani, J.S. Justin, J.A. Meddikar

Conference Highlights /Scientific Contribution

- **Highlights of the 5th GFFCC Conference on Colorectal Cancer, Sharjah, UAE** 72
- **Abstracts of the 5th GFFCC Conference on Colorectal Cancer, Sharjah, UAE** 75
- **News Notes** 87
- **Scientific Activities in the GCC and the Arab World (2nd half of 2011)** 88



Case Report And Review Of Literature: Temporary Asymptomatic Sinus Bradycardia With Carboplatin, Paclitaxel And Bevacizumab: Under-Reported In Clinical Trials And Under-Disclosed In Practice

J. Zekri

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Abstract

Introduction

Paclitaxel, Carboplatin, and Bevacizumab (PCB) is one of the standard chemotherapy regimens for the treatment of non-small cell lung cancer. Temporary asymptomatic bradycardia is recognized toxicity of paclitaxel. However, it is under-disclosed to patients during consent for treatment and is under-reported in clinical phase III trials.

Case report

Here, we report a case of severe but temporary asymptomatic sinus bradycardia (heart rate 39 bpm) in a patient immediately after receiving PCB. The patient was not informed of this

risk during consent to therapy leading to non-compliance with future plan of management. Literature search showed that bradycardia is documented. However, it is not reported adequately in land mark phase III trials' reports.

Conclusion

The cause of bradycardia in this patient is probably paclitaxel. Oncologists should disclose this potential risk to patients during consent to chemotherapy. Investigators should monitor and report it when conducting land mark trials.

Keywords

Asymptomatic Sinus Bradycardia, PCB, CBED, ACCA

Introduction

Many anti-cancer cytotoxic agents (ACCA) have adverse effects on multiple organs and tissues. Adverse effects on cardiac function are well recognized. Cardiac toxicities of ACCA can be transient or permanent, predictable or unpredictable or idiosyncratic or dose related while some are potentiated by the addition of other therapies.

Physicians pay particular attention to effects of ACCA on cardiac muscle function. However, cardiac bioelectric dysfunction (CBED) can be easily missed especially in the outpatient setting.

CBED including bradycardia are recognized adverse effects to some ACCA such as anthracyclins⁽¹⁾, mitoxantrone^(2,3) 5-fluorouracil⁽⁴⁾,

and methotrexate⁽⁵⁾. At times the complexity of anti-neoplastic regimens makes it difficult to identify the culprit agent with any degree of certainty⁽⁶⁾. CBED may occur as one of many manifestations of acute hypersensitivity reactions.

Paclitaxel induces tubulin polymerization and forms extremely stable and non-functional microtubules thus interfering with cell division. It is a broad spectrum ACCA licensed for the treatment of non-small cell lung cancer (NSCLC) in combination with platinum. Bevacizumab, a potent vascular endothelial growth factor (VEGF) inhibitor antibody, is proven to improve survival of patients with NSCLC when combined with paclitaxel and platinum regimen⁽⁷⁾. CBED including bradycardia have been reported with the use of paclitaxel. However, it is not a well-recognized association with the use of bevacizumab.

Here we report the development of

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	10 Feb 15:13	11 Feb 06:08	08:00	11:15	15:02	20:00	21:00	12 Feb 00:05	02:01	04:30	08:00	12:00
Pulse	79	71	42	60	80	41	55	48	43	45	55	54
SBP	130	137	108	128	116	120		135		130	115	122
DBP	90	84	63	84	67	75		76		73	62	83

Table 1: Pulse and blood pressure chart during admission

Pulse expressed as beat per minute, Blood pressure expressed as mm/Hg.

SBP=Systolic blood pressure, DBP=Diastolic blood pressure.

temporary asymptomatic sinus bradycardia in a patient receiving paclitaxel, carboplatin and bevacizumab (PCB) for the treatment of NSCLC. The patient was not prepared for this potential uncommon adverse effect. This impacted adversely on the patient's compliance with treatment.

Case Report:

An otherwise healthy gentleman diagnosed in January 2005 with a stage IIIA NSCLC (adenocarcinoma). He received neoadjuvant carboplatin and docetaxel achieving partial response without any significant toxicity. In particular there was no significant abnormalities of pulse rate (PR) and blood pressure (BP) during and shortly after each cycle of treatment. This was followed by surgical resection. The surgical pathology showed no pulmonary parenchymal viable tumour. However, adenocarcinoma cells were seen in the resected chest wall and ribs. This was followed by adjuvant radiotherapy. In March 2007 he developed multiple bone metastases in the right ribs including the rib remnants. He received 4 cycles of cisplatin and gemcitabine with stable disease. In November 2008 he developed progression in bone metastases. Further systemic therapy was discussed. After 3 months he decided to receive treatment. Inpatient admission for one night to the oncology ward was arranged to receive the first cycle of PCB on 10/02/2009. Routine admission history and physical examination did not reveal any unexpected findings. The treatment regimen was as follows: Paclitaxel 175 mg/m² (total 350 mg),

carboplatin (total 600 mg) and bevacizumab 10 mg/Kg (total 750 mg). Routine taxane premedication and anti-emetics was employed (dexamethasone, ranitidine, diphenhydramine and granisteron).

PR and BP 5 minutes prior to start of chemotherapy were 97 bpm and 130/90 mmHg respectively. He completed treatment at 20:00 and tolerated all the components of chemotherapy regimen well. In particular there was no hypersensitivity or cardio-vascular signs or symptoms. At 08:00 11/2/2009 (12 hours after completing chemotherapy) and in the absence of any symptoms, the nurse recorded the first significantly abnormal physical signs. PR and BP were 42 bpm and 108/63 mmHg. Over the next 16 hours (until 12:00 12/2/2009) the PR remained low at bradycardia rates and the BP remained at relatively lower level in absence of any related symptoms (Table.1). During this period, body temperature, creatinine kinase and troponin levels were normal and O₂ saturation

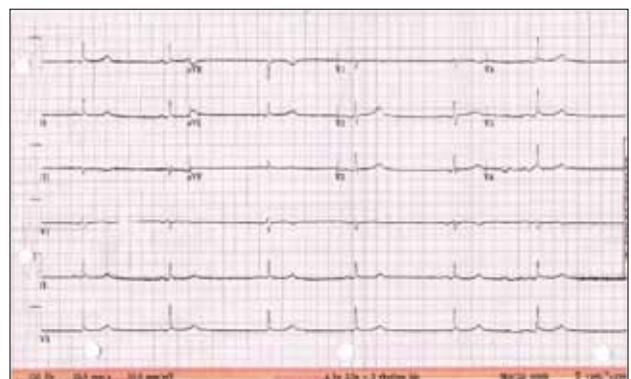


Fig. 1: Electrocardiogram after clinical detection of bradycardia

remained within normal range (96-100%) on room air. However, electrocardiography ECG at 08:50 confirmed sinus bradycardia at rate of 39 bpm (Figure 1). On 12/2/2009 at 13:00 the patient discharged himself against medical advice. He refused booking for a next cycle with the same chemotherapy regimen. However he accepted next day a referral to cardiologist. Two days later elective Holter cardiac rhythm monitor showed no abnormality and pulse rate returned to normal. The patient was lost to oncology follow up.

Discussion

Our patient enjoyed a relatively long 4 years period of disease control with good quality of life and performance status. This encouraged the treating team to consider further systemic therapy to treat the progression in bone metastases.

In view of previous response to a docetaxel based regimen and he was not exposed to the novel targeted agent bevacizumab⁽⁷⁾, further systemic therapy with PCB was offered. The side effects of this regimen were discussed in great detail with the patient. However, cardiac toxicity from the chemotherapy agents in this regimen (paclitaxel and carboplatin) was not discussed.

Due to well documented risk of hypersensitivity reactions, the standard care at our hospital is to admit patients overnight for the first cycle of taxane based regimens. Acute cardiac toxicity including CBED from paclitaxel and carboplatin regimen was not experienced in any patient treated with this regimen at our hospital despite standard careful in-patient monitoring of vital signs for at least 24 hours during the first cycle. This may be one reason for not discussing this potential toxicity with this patient and generally in most other patients during the procedure of consent to this regimen. Other potential reasons include (a) perception of relatively scarce reports describing acute cardiac toxicity and CBED with these drugs (b) during the consent procedure, the discussion is mainly concentrated on what perceived as more serious side effects such as myelo-suppression and neurotoxicity (c) time constraints in busy clinics (d) lack of dedicated pre-administration chemotherapy education clinics.

Careful literature search reveals CBED including bradycardia is a well-documented observation in patients undergoing paclitaxel treatment. At earlier stage of paclitaxel clinical development, a Phase II study of 45 patients with ovarian cancer (all evaluable for toxicity), 13 (29%) developed bradycardia with 2 patients progressed to heart block⁽⁸⁾. Similar rate of bradycardia was reported with paclitaxel from the initiation of NCI-sponsored clinical trials through August 1992. In patients without significant cardiac risk factors, asymptomatic sinus bradycardia is frequent (30%). Heart block and conduction abnormalities occur infrequently and are often asymptomatic⁽⁹⁾. The authors concluded that routine cardiac monitoring is not required for patients without risk factors. There are, however, insufficient data to make treatment recommendations for patients with cardiac disease and those taking medications that alter cardiac conduction. Physicians who administer paclitaxel should continue to be alert to the associated cardiac toxicities. In rare cases myocardial ischemia and infarction have been reported⁽⁹⁾.

A meticulous study reported by Kietpeerakool, C. et. al. evaluated the patterns of ECG, cardiac risk factors and its clinical consequence in 79 women with epithelial ovarian cancer who received paclitaxel and carboplatin (PC) as front line chemotherapy. Among 70 women with normal initial ECG, 8 (11.4%) had sinus tachycardia, 1 (1.4%) had early depolarization, 2 (2.9%) had sinus bradycardia and 3 (4.3%) had sinus arrhythmia in subsequent ECG. All these cardiac disturbances were asymptomatic and needed no intervention. Among 9 patients with abnormal ECG before the first course of PC, 6 (66.7%) had subsequent abnormal ECG but all were asymptomatic and no worsening of abnormal ECG pattern was noted⁽¹⁰⁾.

Our patient had no history of cardiovascular disease. However, he is a chronic smoker and subclinical cardiac dysfunction may exist. On the other hand it is highly unlikely that he had pre-existing CBED as the Holter monitor result 48 hours after the incident was normal. Asymptomatic self-limiting bradycardia

experienced by our patient seems to be similar to what is described in the literature^(8,9,10).

Cardiac toxicity mainly muscle dysfunction of anthracyclins may be enhanced when administered with paclitaxel⁽¹¹⁾. Our patient received carboplatin in the regimen. We found no evidence in the literature to suggest that carboplatin can solely cause bradycardia. Cisplatin, another platinum compound has been reported to cause marked sinus bradycardia, including a patient with a heart rate of 35/min that recurred during each of six cycles of cisplatin^(12,13). Side effects of bevacizumab include systemic arterial hypertension (SAH). It is well known that long term SAH can lead to cardiac function impairment. However, we found no verifiable evidence in the literature to suggest that bevacizumab can solely cause bradycardia. A small trial of 62 patients randomized to irinotecan, fluorouracil with or without bevacizumab reported that Bevacizumab was associated with hypertension and bradycardia⁽¹⁴⁾. The results of this trial were reported in Chinese. We were unable to extract more information from this report due to language barrier.

Generally there is lack of documentation of transient and non-serious cardiac side effects in reports of large Phase III trials investigating chemotherapy in patients with NSCLC. A landmark Phase III trial comparing 4 platinum doublet combinations in NSCLC including carboplatin and paclitaxel in one arm did not document cardiac toxicity⁽¹⁵⁾. It is not clear whether cardiac toxicity was not monitored or there were no significant events worth reporting.

A Phase III trial compared cisplatin and etoposide (EC) with 2 dose levels of paclitaxel in combination with cisplatin. Fatal cardiac events, which were possibly related to treatment, were observed in 0.5% of patients on EC, in 0.5% of patients on high dose paclitaxel, and in 2% of patients on lower dose paclitaxel⁽¹⁶⁾. However, non-fatal events were not documented in the report.

The landmark Phase III trial confirmed improved survival of patients with NSCLC when bevacizumab is added to paclitaxel

and carboplatin⁽⁷⁾. In this trial 3 patients in the bevacizumab arm died of cardiac events that were not considered to be related to the treatment: a myocardial infarction 40 days after the last dose of bevacizumab, a sudden death (no autopsy) during the 18th cycle of treatment, and cardiac arrest with bradycardia after the third cycle (no autopsy). The report did not present other less serious cardiac events. 2% risk of supraventricular tachycardia appears in the manufacturer product leaflet when bevacizumab is combined with 5-fluorouracil and leucovorin. However, bradycardia does not appear in the leaflet.

Conclusion

Temporary asymptomatic sinus bradycardia with PCB is most likely a side effect of paclitaxel. Bradycardia with paclitaxel is not uncommon but usually not serious. To avoid apprehension on the potential occurrence of bradycardia, it should be disclosed to patients during the process of consent to chemotherapy. Investigators should consider reporting less serious side effects including temporary asymptomatic CBED.

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